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CIRCULATORY STUDIES ON ANOXEMIA IN MAN WITH RESPECT TO POSTURE AND CARBON DIOXIDE *

By E. GELLHORN, M.D., PH.D., *Chicago, Illinois*

Mosso,[22] Margaria,[20] Childs, Hamlin and Henderson [4] noted that the effects of anoxemia can be alleviated by breathing low concentrations of CO_2. In several studies (Gellhorn [7, 8]) we have confirmed and extended these observations on a quantitative basis. It was shown in particular that the effects of anoxemia on various processes occurring in the human central nervous system can be offset by inhaling 3 per cent CO_2 during the period of anoxemia. This effect was thought to be due mainly to circulatory and respiratory adjustments. This idea is supported by the fact that under the influence of CO_2 the circulation through the brain is specifically increased (Cobb and Fremont-Smith,[6] Lennox and Gibbs,[19] Gibbs, Gibbs and Lennox,[12] and Schmidt [24]). Furthermore, due to increased muscle tonus, there is an improvement in general circulation indicated by a rise in venous pressure (Henderson and collaborators [14]). Other factors will be discussed below.

The present investigation was undertaken with the aim of establishing, in the human, direct proof for the improvement of the general circulation by CO_2 under the conditions of oxygen deficiency. Since the circulation in the brain, in which the symptoms of oxygen deficiency become first manifest, is primarily dependent on the systemic blood pressure, comparative blood pressure studies on the effect of oxygen deficiency with and without the simultaneous administration of CO_2 seemed appropriate. The fact that under ordinary circumstances oxygen want causes only very slight changes in the systemic blood pressure (Raab,[23] Gellhorn and Spiesman,[9, 10] Christensen and Krogh,[5] and Herbst and Manigold [15]) does not invalidate this argument. In order to show the influence of one particular factor on the blood pressure which is normally maintained by the integrative action of several peripheral and central nervous factors and by the O_2—and CO_2—tension of the blood,

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it seemed appropriate to study the circulatory system under a certain strain which might make the whole system more labile. If such a condition were found it was not improbable that the beneficial effect of CO_2, which was so distinct in our investigations on various functions of the central nervous system under the influence of oxygen want, would also become evident in regard to blood pressure.

As we now know, the maintenance of the blood pressure is dependent to a large extent on the functioning of carotid sinus and depressor reflexes (Hering,[16] Koch,[18] Heymans [17]). When the pressure falls in the aorta and in the carotid artery these reflexes are evoked and the normal blood pressure is restored. Therefore changes in posture are ordinarily not accompanied by significant changes in systemic blood pressure. Under conditions of oxygen want, however, the blood pressure falls considerably in the erect posture, whereas the same degree of oxygen want does not significantly alter the blood pressure in a recumbent position (Mateeff and Schwarz [21]). For this reason the effect of CO_2 under conditions of oxygen deficiency was studied on humans in the erect posture.

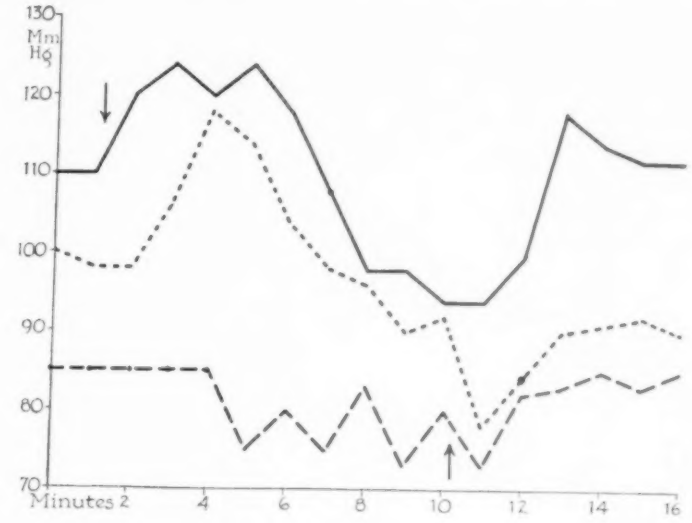
Method

The pulse was counted at one minute intervals and blood pressure readings, systolic and diastolic, were taken by two experimenters while the experimental subject was standing and inhaling a gas mixture from a Douglas bag. The gas mixture was prepared with the aid of a Sargent gas meter and frequently analyzed for O_2 and CO_2. The duration of the experiment was seven to twelve minutes. It was preceded and followed by a control period in which the experimental subject inhaled air. The shift from air to the gas mixture and from that back to air was performed without the knowledge of the experimental subjects. The subjective and objective symptoms observed during the experiments were protocolled immediately after the experiments. The observations were made on 12 healthy experimental subjects, medical students of the ages of 20 to 25, most of whom had served as experimental subjects in experiments in which the effect of O_2 deficiency was studied in regard to various functions of the central nervous system. In some cases the experiments were repeated several times on the same subject without any essential difference in the results.

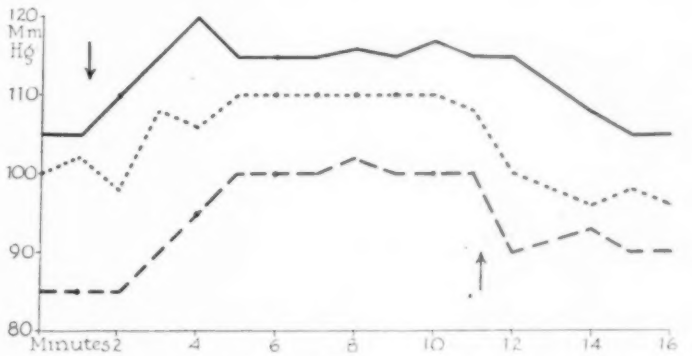
Results

Figures 1a and 1b show the effect of 8.5 per cent O_2, and 8.5 per cent O_2 plus 3 per cent CO_2, respectively, on pulse and blood pressure during a period of nine to ten minutes. In the 8.5 per cent O_2 experiment the systolic blood pressure rises by 10 to 14 mm. mercury during the first three minutes, and then falls gradually below the control value. At the same time the pulse rate which had risen considerably also shows a drop, which even continues for a short time after the readmission of air. The diastolic

blood pressure shows only a slight decrease. All changes were nearly completely reversed in the first five minutes following the period of O_2 want. The characteristic feature of this and similar experiments is the fact that the increase in blood pressure and pulse rate resulting from anoxemia does not persist throughout the experiment but that a collapse-like reaction occurs



1a



1b

FIG. 1a and 1b: 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively between arrows. (Subject He., erect posture.) (FIGS. 1–4 and 6–7: —— systolic blood pressure, - - - - diastolic blood pressure, ... pulse rate per min. Abscissa: time in min., ordinate: blood pressure in mm. Hg and pulse rate per min.)

characterized by a more or less abrupt decrease in systolic blood pressure and pulse rate, accompanied by considerable weakening of the pulse, pallor and dizziness. In some experiments showing the same type of reaction a sudden collapse sets in and the pulse becomes imperceptible but the recovery is fast.

Comparing with this experiment the results obtained from the same subject under the conditions of the same degree of oxygen want, but in the presence of 3 per cent CO_2, we see an enormous contrast (figure 1b). The systolic blood pressure is slightly elevated and remains so throughout the whole period of O_2 want. The changes in pulse rate are slight, but the increase observed also persists until air is readmitted. The diastolic blood

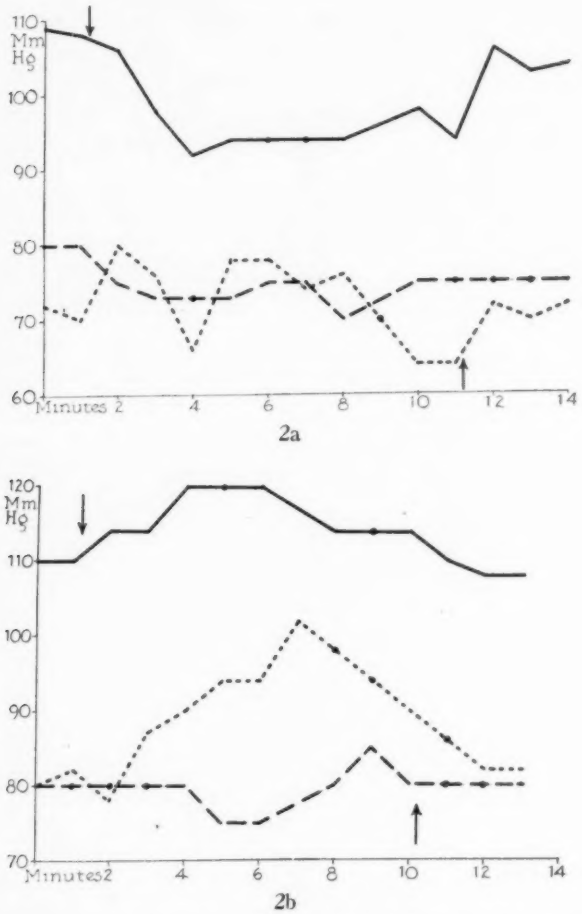
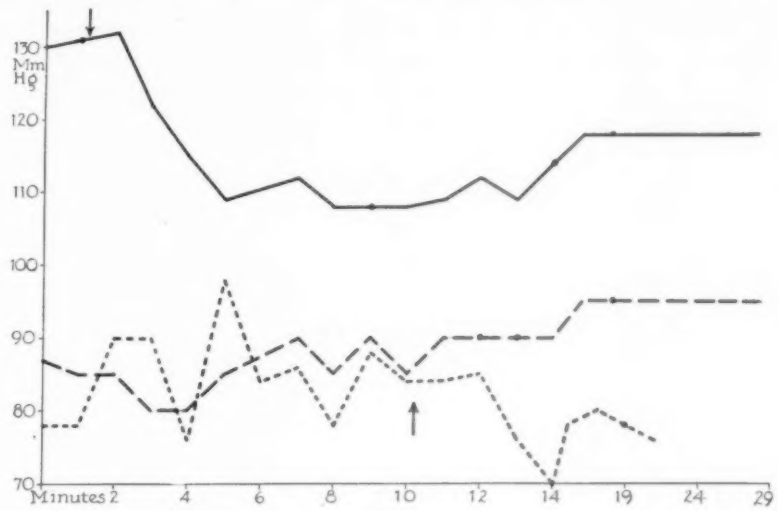


FIG. 2a and 2b: 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively between arrows. (Subject Fa., erect posture.)

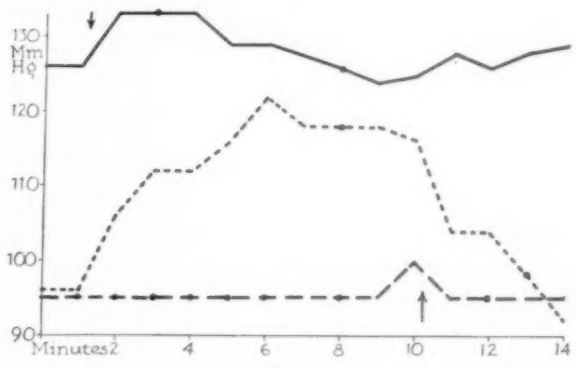
pressure shows an increase during the experiment. The subjective experiences of the subject are equally striking. In general the subjects feel fairly well except for a slight dizziness or feeling of warmth. In some cases no symptoms whatever are observed, even though certain of these cases had experienced severe symptoms in the absence of 3 per cent CO_2.

Figure 2 represents the record of an experiment in which the circulatory adjustment under oxygen want is still poorer than in the first case (figure 1).

After admission of 8.5 per cent O_2 in erect position the systolic blood pressure gradually falls and remains fairly low during the period of anoxemia. The pulse rate shows irregular variations without any definite tendency. The diastolic blood pressure is practically unaltered. In contrast to this reaction we observe, in the corresponding oxygen deficiency experiment in which 3 per cent CO_2 was also administered, that the fall in blood pressure is



3a



3b

FIG. 3a and 3b: 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively between arrows. (Subject St., erect posture.)

not only completely prevented but that the blood pressure remains elevated throughout the experimental period. Furthermore, a distinct increase in pulse rate occurs during this time.

A very similar type to that shown in figure 2 is illustrated in figure 3. The main difference between the two experimental subjects is the fact that the systolic blood pressure is considerably higher to begin with in the case

of subject S (figure 3) than in that of F (figure 2). It is striking to see that the systolic blood pressure falls continuously until it reaches a certain equilibrium and that permanent changes in pulse rate are absent in anoxemia, whereas in the presence of 3 per cent CO_2 a marked increase in pulse rate occurs and the fall in systolic blood pressure is completely prevented. The difference in the two subjects whose curves are illustrated in figures 2 and 3 is, as was mentioned, a difference in the absolute values for the systolic pressure. This seems to be of considerable importance. S, whose systolic blood pressure is considerably greater than that of F, shows far less symptoms than the latter, obviously for the reason that the circulation of the brain can be maintained to a better degree in the first case than in the second,

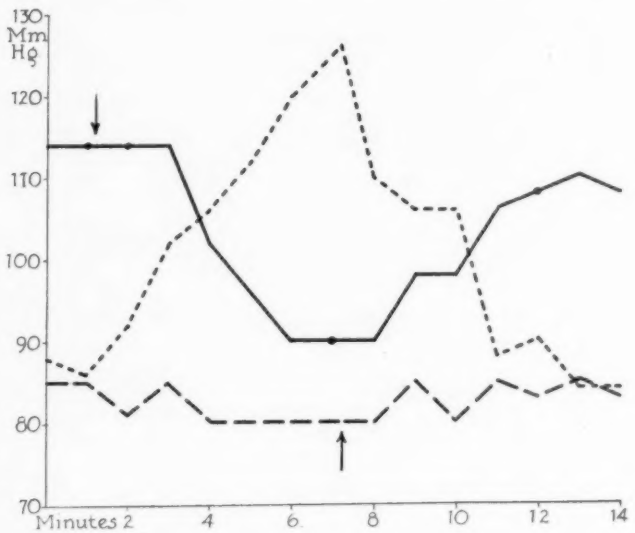


FIG. 4: 8 per cent O_2 between arrows. (Subject G., erect posture.)

since, as it is well known, the degree of circulation through the brain is largely dependent on the level of the systemic blood pressure (Starling [26]).

The experiments discussed so far have one feature in common, namely, the fall in the systolic blood pressure during anoxemia is accompanied by a decline in the pulse rate or by a complete failure of the organism to increase its pulse rate under anoxemia. But this is not always the case. Figure 4 shows a record in which a very marked drop in systolic blood pressure occurs during anoxemia which produces a condition approaching collapse, while at the same time the pulse rate increases tremendously. We are probably not mistaken in assuming the circulatory conditions in this case to be similar to those described in the other experiments, since in both types of reactions collapse may ensue. That a very rapid pulse is associated with a decrease in minute volume, has frequently been shown to be true under conditions of oxygen want (Barcroft [2]).

As the description of various experiments has shown, the main difference in the experiments with 8 and 8.5 per cent O_2 with and without 3 per cent CO_2 lies in the fact that the systolic blood pressure falls in anoxemia to a relatively low level, thereby endangering the blood circulation through the brain. In the presence of 3 per cent CO_2, however, this reaction is more or less completely prevented, and the systolic blood pressure remains either normal or even slightly elevated. A summary of several such experiments is presented in figure 5.

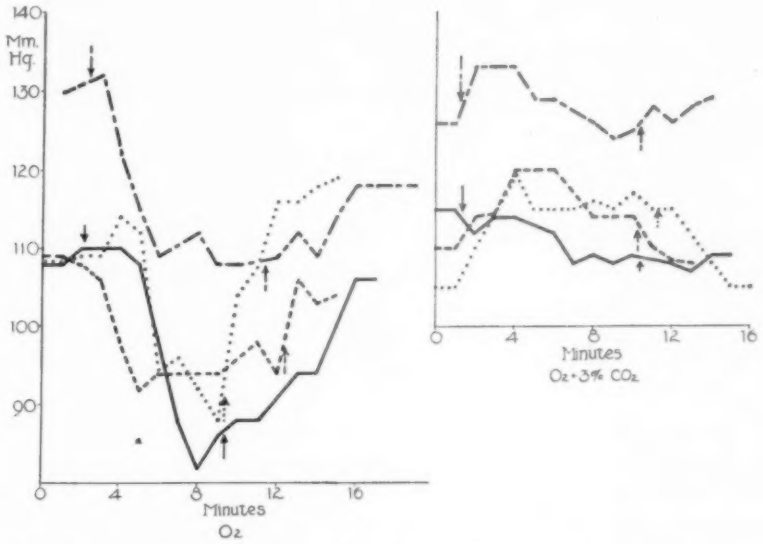
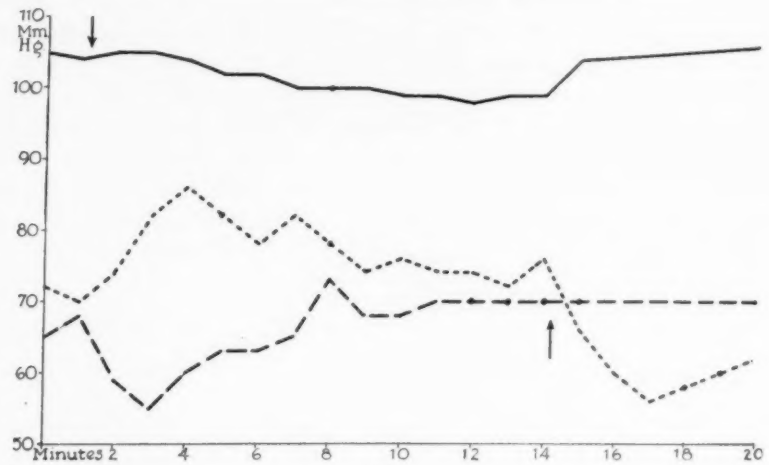


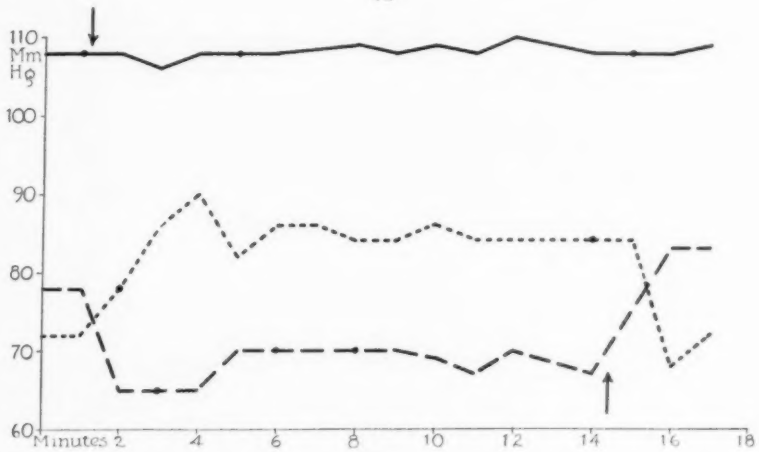
FIG. 5: The effect of 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively on four different subjects in erect posture.

Figure 6 represents an experiment carried out on subject F, whose record was shown in figure 2. The only difference between the two experiments is that, while F is standing throughout the whole experiment illustrated in figure 2, he is lying down in the experiment recorded in figure 6. The difference in the reaction of the blood pressure is evident from the comparison of the two records. Equally marked are the differences in the subjective symptoms. Practically all experimental subjects have very little or no complaints whatever during the recumbent position even in those cases where they actually faint or are brought very near to this state in the erect position. As figure 6 indicates, the systolic blood pressure remains practically unaltered. However, a very slight tendency toward a fall is still present in the pure oxygen deficiency experiment and absent in the corresponding experiment with 3 per cent CO_2. The experiments carried out with other subjects in recumbent position are very similar and, therefore, omitted. The results justify the statement that characteristic differences in blood pressure occur during oxygen deficiency with and without 3 per

cent CO_2 in the erect position of the experimental subjects, whereas in the recumbent position no such differences in blood pressure exist.



6a



6b

FIG. 6a and 6b: 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively between arrows. (Subject Fa., *lying down.*)

DISCUSSION

The first question to be answered is the rôle of acapnia in the differences existing in the oxygen deficiency experiments with and without the presence of 3 per cent CO_2. It is, of course, clear that in the absence of CO_2 the increased respiration resulting from O_2 want leads to a certain degree of acapnia, and it is known, from numerous papers of Henderson,[13] that under the influence of acapnia the venous return to the heart is diminished and that, consequently, the systolic blood pressure decreases. The question is to decide what importance must be attributed to this factor under the conditions

of our experiments. Therefore a series of experiments was performed in which the experimental subjects voluntarily increased their respiratory volume to a degree similar to that observed under conditions of O_2 want. As table 1 indicates, the greatest drop in blood pressure observed under these

TABLE I

Maximal Decrease in Blood Pressure in the Erect Position

A. Under O_2 Want				
Ste.	132	116	—12%	
Hei.	109	88	—19%	
Jen.	108	82	—24%	Average —17.4%
Lam.	108	96	—11%	
Gol.	114	90	—21%	
B. Under the Influence of a Hyperpnea Similar to That Occurring in O_2 Want				
Ste.	122	112	—8%	
Hei.	119	114	—4%	
Jen.	109	107	—2%	Average —4%
Lam.	106	102	—4%	
Gol.	106	104	—2%	

conditions is negligible in comparison to the decrease in blood pressure present in our O_2 want experiments. It may, therefore, be said that a certain degree of acapnia may have almost no effect on the systolic blood pressure when the oxygenation of the blood remains normal. If, however, oxygen deficiency and acapnia are combined, as was the case in the main experiments described in this paper, the reduction in blood supply to the brain, resulting from the acapnia (Cobb and Fremont-Smith,[6] Schmidt[24]), aggravates the condition of anoxemia in the central nervous system to such a degree that the blood pressure falls, particularly when the erect posture favors anoxemia of the brain.

Although we believe, as will be shown later, that the major rôle in the decrease of blood pressure observed under conditions of O_2 want in erect posture is played by the carotid sinus, it is to be expected that the vasomotor center as such is of considerable importance. If this is the case the results mean that the loss of CO_2 interferes with the maintenance of the normal tonus of the vasomotor center more under the conditions of anoxemia than under conditions of normal oxygenation of the central nervous system. This implies that CO_2 increases the blood pressure more in anoxemia than under control conditions. This inference has been tested directly in dogs in as yet unpublished experiments (Gellhorn and Lambert[11]) and shown to be true. Carbon dioxide increases considerably the blood pressure in dogs which are subjected to O_2 want, although the same concentration of CO_2 may not have any effect on the blood pressure as long as the dog is breathing air.

What then is the final mechanism of the difference in blood pressure under conditions of O_2 want in the absence and in the presence of 3 per cent CO_2? Since the blood pressure records show no significant differences in the two conditions in a recumbent position, it must be inferred that the main

factor producing these differences is elicited by the erect posture. Now we know that if we change from the recumbent to the erect position there is a temporary decrease in blood pressure in the carotid artery. This, in turn, brings about a restoration in the blood pressure due to the carotid sinus (and aortic nerves) reflexes. It seems, therefore, that under the conditions of anoxemia these reflexes do not function satisfactorily and that CO_2 is a very potent factor to restore them to normality.

The syndrome which we have observed is similar to that of orthostatic hypotension. Here too the change from the recumbent to the erect posture leads to a very considerable drop in blood pressure. The investigations of Alvarez and Roth (1935) have shown that the efferent path of the sympathetic seems to be somewhat affected, at least in one of the cases studied, and this could at least partially account for the decrease in blood pressure in the erect position. The authors, however, feel that these changes are not sufficient to account for the complete syndrome and mention the possibility "that in this disease of orthostatic hypotension there is some defect in the blood pressure regulating mechanism situated in the carotid sinus, but as yet there is no information on that point." The importance of this mechanism is apparent from clinical observations on hypersensitivity of the carotid sinus when under the influence of mechanical stimulation of the carotid sinus a decrease in systolic blood pressure occurs (Smith [25]). On the basis of these observations and of our own findings, we think it very probable that the carotid sinus mechanism is deficient under O_2 want, due to an insufficient oxygenation of the centers involved, and that the restoration of the circulation in the presence of CO_2 restores these reflexes sufficiently to prevent a fall in blood pressure.

These considerations make it very probable that the carotid sinus (and possibly the aortic nerves) are of primary importance in the explanation of the blood pressure differences observed under conditions of O_2 want with and without CO_2 in the erect position. But we do not believe that this mechanism explains completely all the subjective and objective differences under the two conditions, since characteristic differences remain, at least to a certain extent, even in the recumbent position. In spite of the fact that a certain degree of O_2 want in the erect posture may produce severe headache, weakness, dizziness, a feeling of fullness of the head, paresthesia, impaired vision and hearing and occasionally nausea, it may cause practically no symptoms in the reclining position whether CO_2 is present or not. Not infrequently, however, cases are observed in which the same degree of O_2 want does produce symptoms of slight dizziness, feeling of warmth and disturbances of special senses (the objects in the room appear darker or purplish, the hearing is slightly impaired) in the recumbent position whereas no symptoms may be elicited in the added presence of 3 per cent CO_2. This difference is, of course, due to the fact that 3 per cent CO_2 improves the oxygenation of the tissues in general and of the brain in particular. It does so by

1. An increase in the respiratory volume.
2. The right shift in the oxygen dissociation curve (Barcroft [3]).
3. The improved venous return due to the increased muscular tonus (Henderson, Oughterson, Greenberg and Searle [14]).
4. The specific effect of CO_2 on the blood vessels of the brain (dilatation), (Cobb and collaborators [6, 12, 19]).
5. The increased sensitivity of the vasomotor center to CO_2 under conditions of oxygen want (Gellhorn and Lambert [11]).

Summary

The influence of O_2 want (8 to 8.5 per cent O_2) with and without 3 per cent CO_2 has been studied in the human in the erect and recumbent positions with respect to blood pressure and pulse rate. The results are as follows:

1. In the recumbent position there are practically no differences between the periods of O_2 want and O_2 want plus 3 per cent CO_2. The blood pressure remains unchanged. The pulse rate is slightly increased in either case.

2. In periods of O_2 want the systolic blood pressure shows, in the erect position, a temporary rise which is followed by a fall below the control values. This fall may lead eventually to collapse. In the presence of CO_2 this is prevented and the systolic blood pressure remains elevated throughout the whole period of O_2 want.

3. The changes in diastolic blood pressure are not constant. The pulse rate shows great variability; in most subjects it follows the blood pressure changes. Collapse may, however, occur even during periods of maximally increased pulse rate.

4. The subjective symptoms of anoxemia are more severe in the erect than in the recumbent position. CO_2 may, in either position, completely prevent, or at least greatly diminish, the occurrence of anoxemic symptoms.

5. The aggravation in subjective and objective signs of anoxemia, if the experiment is carried out in the erect position, is thought to be due to the failure of the carotid sinus reflexes under the conditions of oxygen deficiency. The addition of 3 per cent CO_2 to the O_2 deficient gas mixtures under these conditions seems to exert its beneficial effect on the objective and subjective signs by improving the oxygenation of the medullary centers and thereby restoring the carotid sinus reflexes to normal.

6. The effect of a certain degree of acapnia on blood pressure is much greater under anoxemic than under normal conditions.

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DEATH COMPLICATING THE WITHDRAWAL OF NARCOTICS, WITH RESPIRATORY DIFFICULTIES PREDOMINANT: REPORT OF THREE CASES *

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DURING the past three years we have seen three dramatic deaths in narcotic addicts who had been suddenly deprived of the drugs to which they had become habituated.

A search through the literature for descriptions of and explanations for such occurrences has been singularly unproductive.‡ In writing on the subject of morphine withdrawal, many authors have commented on the possibility of collapse, particularly as a complication of sudden withdrawal. Their comments, however, have been uniformly casual and incidental; and in no instance have we been able to discover a specific case report. Several general descriptions of the symptoms likely to occur in such collapse were noted; but here again the literature proved disappointing, since none of these brief general references to the manner of death in this type of case mentioned the occurrence of any outstanding respiratory symptom and since practically all of them spoke chiefly of circulatory collapse. It is because of an unusual finding in connection with the respiration in all three of our cases, the absence of circulatory collapse except just before death, and the scarcity of reported detailed material regarding such cases, that this report is being made. On the occasions when our cases were under observation, we had no thought of publishing data concerning them; so that the laboratory investigations were not as numerous as they otherwise might have been. Only one of the cases was studied in some detail. We submit this report with the hope that interest in the subject will be stimulated, and that more information regarding it will be forthcoming.

CASE REPORTS

Case 1. F. H., white male, aged 44; admitted May 7, 1936. The patient had been in the hospital on three previous occasions, the first time in order to break the morphine habit, the next two times to be "cured" of paregoric addiction. In each instance sudden withdrawal was accomplished in a thoroughly satisfactory manner

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‡ Personal communications from Hans Schwarz of Berlin, Germany, and Manfred Sakel of Vienna, Austria, inform us that those investigators, despite much contact with the subject of morphinism, know of no pertinent information regarding sudden death in this connection, either from their own clinical observation or their acquaintanceship with the literature. We would also like to acknowledge the assistance of Dr. Fritz Moellenhoff, whose knowledge of the foreign literature on the subject was of much help in surveying the field of available information.

with the aid of insulin and ordinary sedatives. Previous to the hospitalization under discussion he had been taking large quantities of paregoric regularly for almost a year. During the two weeks previous to admission, in anticipation of another "cure," he had diminished his paregoric ingestion to two to three ounces per day; and in addition, he had obtained 10 to 15 units of insulin three times per day from his private physician during this two week period.

He was admitted to the ward at 7:30 p.m., walking. He had no subjective complaints other than of a feeling of mild apprehension. He had had his last dose of paregoric at about noon of the day of admission. Physical examination revealed no significant findings except for moderate malnutrition. He was given 15 units of insulin one hour after admission, and 3 drams of paraldehyde one hour later, shortly after which he fell asleep. His sleep, checked at half-hour intervals, was normal until 2:30 a.m.—seven hours after admission, and about 18 hours after his last dose of paregoric. At this time he was found in coma. The significant findings were as follows:

Physical: Temperature 102° F.; pulse 80; respiration 48. Respiration peculiar (described under Comment). Pupils dilated and fixed to light. Pulse regular, of good quality. Pulmonary edema. Generalized cyanosis. Blood pressure normal. No significant neurologic findings, save those that would be expected in profound coma. No response to painful or other stimuli. The pulmonary edema responded to atropine.

Urine: Clear, amber; sp. gr. 1.030; albumin negative; sugar negative; acetone mildly positive. Microscopic examination negative. *Blood:* Wassermann test negative. Red blood cells 3,900,000; hemoglobin 85 per cent; white blood cells (24 hours after onset of coma) 32,000, with 84 per cent polymorphonuclear leukocytes, 2 per cent lymphocytes, 1 per cent monocytes, and 13 per cent metamyelocytes. CO_2 combining power—16 vol. per cent (4 hours after onset of coma). Urea nitrogen, 21 mg. per cent (4 hours after onset of coma). Sugar, 235 mg. per cent (two hours after intravenous glucose). Phosphorus 2.5 mg. per cent. Chlorides 490 mg. per cent. Non-protein nitrogen 25.6 mg. per cent.

Spinal fluid: Clear, colorless; moderately increased pressure. Globulin normal. Cells normal. Sugar 110 mg. per cent (2 hours after intravenous glucose). Chlorides 750 mg. per cent. Wassermann test negative.

Roentgen-ray of chest: (19 hours after onset of coma) negative.

The medications used during the coma were hypertonic glucose intravenously and by hypodermoclysis, physiologic saline by hypodermoclysis, intravenous and intramuscular calcium gluconate, subcutaneous atropine sulphate, caffeine sodium benzoate, and insulin, and intravenous and intramuscular aminophyllin. Morphine was started seven hours after the onset of coma and given in 1/4 to 1/6 grain doses every four hours thereafter, without effect.

Course: The patient remained in coma until death intervened on May 10, 1936. His temperature rose steadily to 107° F., and his pulse rate to 160+. His respiratory rate fluctuated between 30 and 48 per minute. On the second day of the coma he had a generalized convulsion lasting five minutes. Bronchopneumonia was noted several hours before death occurred, and circulatory collapse manifested itself during the last few hours.

Autopsy: Gross findings were lobular pneumonia, toxic changes and chronic passive congestion of the viscera, aortic atherosclerosis, possible early coronary sclerosis, early fatty infiltration of the liver, and cerebral congestion and edema. Microscopic findings were lobular pneumonia, toxic changes in the viscera, early generalized arterio and arteriolar sclerosis, heart negative except for toxic myocardosis, focal necrosis and fatty infiltration of the liver, chronic prostatitis with hyperplasia, cerebral congestion and edema, chronic leptomeningitis, and early degenerative changes in the pons.

Case 2. M. H., white male, aged 36. The patient had been taking 18 grains of morphine intravenously per day. During the week previous to admission to the hospital, he had been drinking excessively, and had not been able to obtain any narcotics. His condition suggested an impending delirium tremens for the first two days in the hospital, and he manifested no symptoms that might have been interpreted as specifically due to withdrawal of narcotics. Two days after admission he was found in deep coma and breathing peculiarly. Physical examination revealed generalized cyanosis, pulmonary edema, marked generalized muscular irritability, and fixed dilated pupils. No other significant physical or neurologic findings were noted. The circulation seemed adequate. Only ordinary delirium tremens treatment (spinal fluid drainage, dehydrants, fluids, caffeine, and ordinary sedatives) had been used previous to the onset of coma. Thereafter, atropine was given as indicated for the pulmonary edema, insulin and intravenous hypertonic glucose were used irregularly, and morphine was administered every four hours. Both the coma and the unorthodox respiration fluctuated irregularly, and seemed to bear no relation to the medications administered. Morphine apparently had no effect. The patient was frequently delirious between comatose periods, and had numerous generalized convulsions. The basic neurologic picture did not change. The temperature rose to 106° F., the pulse to 150, and the respiration to 52, two days after the onset of the coma; thereafter all three subsided to close to normal for a day, and then steadily mounted, the temperature to 108°, the pulse to 160+, and the respirations to 64. At this time, six days after the onset of coma, evidences of terminal bronchopneumonia and circulatory collapse were observed and were followed shortly by the patient's death. The blood and spinal fluid tests gave no evidence of syphilis. An autopsy was not performed.

Case 3. E. P., a white male, aged 49, had been taking 1½ grains of heroin intravenously per day. He took his last dose three days prior to hospitalization. On admission at 12:30 a.m. he was found to be in good physical and mental condition, and complained only of cramp-like pains in the abdomen. He was given paraldehyde, and soon was sleeping peacefully. At 3:30 a.m. (three hours after admission) his unusual respiration was noted, and he could not be aroused. Stimulants were given without effect. No other medications were given during the patient's stay in the hospital. Morphine was not administered. He died two hours after the onset of coma. Autopsy was not done. No further details were reported on the patient's record.

Comment

In the cases reported, the outstanding clinical manifestations common to all three were coma, an unusual respiratory disturbance and death. We would like to call attention again to the respiratory phenomenon, for which we can offer no explanation. The respiration was irregular in rhythm and uniformly deep. Periods of apnea of varying lengths (up to 1½ minutes) occurred at irregular intervals, to be followed immediately by deep, gasping inspirations during which all the accessory muscles of respiration were put to vigorous use. The expiratory phases were not particularly forceful. Generalized cyanosis was quite marked. These dyspneic periods fluctuated in duration in the same patient, lasting from five minutes to several hours. During the intervals between the attacks of dyspnea, which also varied in length, the cyanosis diminished. The administration of morphine sulphate subcutaneously had no appreciable effect. It was thought that subcutaneous caffeine-sodium-benzoate occasionally lessened the respiratory distress for

short periods. Though the respiration suggested the Cheyne-Stokes type of breathing in some respects, it was by no means typical. All the clinicians who observed these cases agreed that the respiratory difficulty was almost certainly central in origin. Gross and histologic study of the medulla on postmortem examination of the only one of these cases that came to the autopsy table revealed no enlightening pathology. Whether the degenerative changes present in the pons offered a significant clue was not clear to us. It is known that the depressing effect of a poisonous dose of morphine on the respiratory center of the frog will eventually result in a type of respiration which is somewhat like that seen in our patients. This fact, however, does not explain why abrupt withdrawal of the poisonous substance should produce a similar result.

Another aspect of the problem which has seemed to us to be worthy of emphasis is the fact that the unusual respiratory behavior was common to the three cases despite the existence in each case of factors which made it distinct from the others. The type of opium derivative to which each was habituated, the time between the patient's last dose of drug and the onset of coma and respiratory difficulty, the non-narcotic medication given before and after the onset of the coma—these and other factors varied markedly in the three cases. To us these differences served to make the common findings stand out even more prominently.

We would also like to point out that the circulatory failure so frequently mentioned in the general discussions in the literature as being an outstanding manifestation of the collapse of narcotic withdrawal, did not occur in those two of our patients concerning whom we have adequate information recorded (save as a terminal phenomenon).

Finally we would like to stress that, contrary to a notion that seems to prevail among many clinicians, withdrawal of narcotics from addicts may be complicated by death sufficiently frequently to indicate first, the need for considerable care in the selection of cases for withdrawal and of the choice of method of withdrawal for individual patients; and second, the necessity for diligent clinical observation of patients during the course of withdrawal.

Summary

1. Three cases are presented, in which death complicated the sudden withdrawal of narcotics from addicts.

2. An unusual respiratory disturbance, common to the three cases, is described.

3. The absence of circulatory collapse in these cases is pointed out.

FATAL IODINE POISONING: A CLINICO-PATHOLOGIC AND EXPERIMENTAL STUDY *

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It is noteworthy that although iodine is used so extensively, comparatively few cases of death through its use have been reported in the medical literature. American medical literature, in particular, contains very few references to either fatal or non-fatal iodine poisoning.

Up to 1911 Witthause [1] found in the literature only 31 cases of poisoning by iodine. Reports from the Westend Hospital in Berlin show that during the years 1912 to 1925, of 1838 cases of poisoning only one instance of iodine poisoning is recorded, the patient recovering.[2] Non-fatal iodine poisoning following the oral administration of iodine-containing dye for gall-bladder visualization has been recently reported by Davis and Ross.[3] A remarkable case of iodine poisoning with recovery is described by Lejbowitsch.[4]

The symptoms of acute iodine poisoning are varied. According to Webster,[5] the local application of an iodine preparation results in a brownish discoloration of the skin with a desquamative dermatitis which may become purulent. When taken internally, the mucous membranes of the mouth, esophagus and stomach are colored brown. The patient vomits a fluid which is usually brownish, but which is colored blue if the stomach contains starches or if the patient is given starch water as an antidote. The bowels move frequently, passing liquid stools, occasionally with mucus. The pulse becomes weak, urinary retention generally results. In fatal cases anuria develops, followed by delirium, stupor and finally collapse.

Bastedo [6] describes an iodide fever which may develop even after the local application of an iodine ointment. A few deaths due to the therapeutic use of iodine have been reported.[7, 8, 9]

Numerous instances of poisoning have occurred due to mistakes in accidentally substituting iodine for other darkly colored medicine. Usually the mistake is noticed immediately and prompt action usually averts a fatal ending.

Suicidal intent is responsible for most of the fatal iodine poisonings. With suicide in mind the individual usually takes a tremendous dose, or else delays calling for help sufficiently long for treatment to be of no avail.

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From the above reports it is apparent that deaths from iodine poisoning fall into three groups:

Group I. Medicinal use; internally, by injection or by local application.

Group II. Ingestion of iodine by mistaking it for another drug.

Group III. Ingestion with suicidal intent.

Studying the records of the Medical Examiner's Office of New York City for the past six years, we found 18 instances of suicide by iodine. Of these cases, 13 were males and five females. Death occurred usually within 48 hours after taking the iodine solution. In two instances death resulted within one-half hour and one hour respectively. One individual died after 52 days, following an operation for stenosis of the esophagus which resulted from the ingestion of the iodine. The amount taken, recorded in only nine cases, varied between one and eight ounces of the tincture.

All 18 cases came to necropsy. A number of anatomical diagnoses were made in each instance but the principal causes of death were as follows:

Pneumonia	six cases
Pulmonary edema	three cases
Cardiac failure	three cases
Asphyxiation	one case
Peritonitis	one case
Acute corrosive gastritis	one case
Acute ulcerative colitis	one case
Acute parenchymatous degeneration of the liver	one case

In one case the direct cause of death could not be determined because of the condition of the body.

Of the few cases reported in the literature, edema of the glottis is mentioned frequently as the cause of death. One patient was saved by a prompt tracheotomy.[10] In our series of 18 patients only one died as a result of asphyxiation.

In four cases no tests for iodine were made. In two cases in which no iodine was found either in the stomach contents or in the liver, one patient had died 12 hours and the other 52 days after the ingestion of iodine. In the remaining cases, iodine was found in the stomach alone six times; in the liver alone twice; in the stomach and liver twice; in the stomach, liver and kidneys once; and in the jejunal contents and liver once. In this case (number 10) an old gastro-jejunostomy opening was found. Of the two cases in which iodine was found in the liver and not in the stomach contents one had died after 49 hours (number 14), the other (number 8), after 61 hours.

Not all of the above cases presented similar pathologic changes. Iodine is a cell poison, although the slowest acting of the halogen group. Because iodine combines readily with starches, proteins and unsaturated fatty acids forming stable combinations, much of the ingested iodine may become bound to any of these food substances present in the stomach. Since such compounds are but poorly and slowly dissociated their toxic effects are lessened or the drug rendered totally inactive. The minimum lethal dose

in man is not known. Death has been caused by 20 grains of iodine, and recovery has followed the taking of 150 grains.[11]

Table 1 gives a résumé of the chief anatomical findings of the 18 cases found in the Medical Examiner's Office. As far as could be ascertained from the protocols the extent of the pathologic changes in the organs bore no relation to the length of time between the ingestion of the drug and death. It will be noted that in all but four cases (numbers 6, 7, 9 and 18) the stomach mucosa was affected, the degree of change varying from simple staining to complete necrosis and edema of the wall. In no instance was there any perforation, although in one case (number 8) the stomach wall was noted as abnormally thinned. In those cases in which the amount of ingested iodine was determinable, there was no parallelism between the amount ingested and the degree of gastric involvement; nor was there any apparent parallel between this and the amount of iodine found in the gastric contents, either as free iodine or in combined form (see case 18). The duodenum was involved 11 times, the degree varying from congestion to widespread mucosal necrosis. As with the stomach, there was no apparent correlation with the amount of iodine ingested. It will, however, be noted that, with the exception of case 14 in which four days elapsed before death, the duodenum was involved only in those cases wherein death ensued within a few hours after the ingestion of the drug. The small intestine showed mucosal involvement in only three instances, while the colon showed ulceration of the mucosa only in the case of a patient who had lived for five days after taking the iodine. In view of the fact, however,. that two other patients in this series survived for longer periods and showed no such colonic lesion this case must be considered exceptional, especially since no similar finding has been recorded in the literature.

The liver showed gross changes in 14 instances. In five cases there was congestion alone, in six gross fatty changes, in four marked cloudy swelling. Histologic examination was available only in our own case (vide infra) in which extensive fatty changes were noted. As with the stomach, the amount of iodine or iodide in the liver could not be correlated with the changes noted. Thus, in case 14, 11.5 mg. of iodine were found in 1000 gm. of a liver that grossly showed fatty changes, while in case 10, with 86 mg. of iodine in 500 gm., the liver was merely congested. In this series of cases, there were apparently no gross changes in the gall-bladders; nor do we find any record of clinical determinations for iodine in gall-bladder bile. That these findings may have been complicated by the treatment given the patient is suggested by case 3. In this case a definite history of iodine ingestion was obtained. At autopsy a severe corrosive gastritis and esophagitis was found, one of the most severe in the entire series, coupled with marked cloudy swelling of the liver. Detailed chemical studies of these viscera failed, however, to reveal any trace of free or combined iodine, or other poison; and it was later learned that repeated intensive

TABLE I

Summary of Gross Pathological Changes Observed in 18 Autopsied Cases Found in Medical Examiner's Office

Case No.	Duration of Life	Amt. Iodine Ingested	Gross Pathological Changes Observed in								Weight of Kidneys	Iodine Found
			Esophagus	Stomach	Duodenum	Small Intestines	Colon	Liver	Gall-Bladder	Kidneys		
1	12 days	Unknown	Discrete hemorrhages, lower half	Mucous membrane dark, hemorrhagic	Not noted	Not noted	None	None	None	Cortex pale	500 gm.	Not examined
2	10 hours	6 ounces	Mucous membrane stained dark brown, flaky and strand-like desquamation near cardia	Scattered hemorrhages in a smooth mucous membrane with absent rugae	None	None	None	None	None	Cortex pale, smooth	300 gm.	None in liver, kidneys, stomach contents
3	13 hours	Unknown	Slate-gray, dry cooked mucous membrane, swollen wall. Mucous membrane easily separable	Gray-blue cooked mucous membrane easily separable; eroded near incisura	Mucous membrane patchy blue-gray; submucosal vessels thrombosed	As for duodenum	None	Glazed, markings not distinguished	None	Congested	205 gm.	None in brain, liver, kidney, stomach contents
4	Few hours	3 ounces	Mucous membrane white, easily separable dry cooked membrane	Mucous membrane extensively corroded esp. along lesser curvature; light gray, granular easily separable membrane	Gray, friable mucous membrane	As for duodenum	None	Congested, markings indistinct	None	Congested	Normal	Large amounts combined iodine (iodide) in gastric contents; no free I; other organs not examined
5	Few hours	Unknown	Not noted	Edematous, congested wall; mucous membrane thickened, gray black	Patchy necrosis of mucous membrane with extensive intramucosal hemorrhages	None	None	Flabby, fatty, markings indistinct	None	Markedly congested	200 gm.	Not examined
6	52 days	Unknown	See detailed report in text	None	None	None	None	Fatty	None	Congested	370 gm.	Not examined
7	38 hours	3 ounces	Not noted	None	Not noted	Not noted	Not noted	Normal	None	Pale cortex, markings indistinct	Normal	No iodine or iodide in liver and kidney
8	2 days	3 ounces	Mucous membrane largely necrotic; wall reddened, thinned	Mucous membrane necrotic, yellow-brown especially along lesser curvature; wall markedly thinned	None	None	None	Fatty	None	Pale cortex	360 gm.	Fairly large amount of iodide in liver
9	5 days	1 ounce	Not noted	Normal mucous membrane and wall	None	None	Ulcerative colitis	Glassy, fatty	None	Pale, edematous	Somewhat enlarged	Not examined

TABLE I—*Continued*

Case No.	Duration of Life	Amt. Iodine Ingested	Gross Pathological Changes Observed in								Weight of Kidneys	Iodine Found
			Esophagus	Stomach	Duodenum	Small Intestines	Colon	Liver	Gall-Bladder	Kidneys		
10	4 hours	Unknown	None	Submucosal hemorrhages	Terminal duodenum and adjacent 4 ft. of jejunum acutely inflamed; mucous membrane covered by extensive gray, friable, separable membrane. Case had had antecedent partial gastrectomy		None	Congested, markings indistinct	None	"Old chronic nephritis"	Not noted	Liver, 86 mg. iodide in 500 gm. tissue. Jejunal contents, 122 mg. free iodine in 20 c.c.
11	Unknown	Evidently 8 ounces	None	Corroded mucous membrane	Autolytic mucous membrane	None	None	Autolytic	Autolytic	Autolytic	Not noted	Liver, 34.5 mg. iodide in 500 gm. tissue. Kidney, 5.6 mg. iodide in 100 gm. tissue. Stomach, 156 mg. iodide in total
12	1 to 1½ hours	Unknown	Not noted	Mucous membrane necrotic throughout	Congested	None	None	Congested, markings indistinct	None	Congested	Not noted	Not examined
13	2 days	1 ounce	Not noted	Mucous membrane stained brown throughout; occasional petechial hemorrhage	Not noted	Not noted	None	Congested, markings indistinct	None	Cortex pale, indistinguishable from medulla	Not noted	Absent in kidney
14	4 days	2 ounces	Mucous membrane patchily eroded	Mucous membrane markedly swollen, hemorrhagic	Congested	None	None	Congested, fatty	None	Cortex swollen, markings indistinct	"Enlarged"	Liver, 21.5 mg. iodide in 500 gm. tissue
15	3 hours	Unknown	Not noted	Mucous membrane gray-brown, soft, not eroded	Congested	None	None	Congested	None	Cortex swollen, markings indistinct	Not noted	Free iodine present in fairly large amts. in gastric contents. Iodides present in fair amts. in liver
16	1 hour	¼ pint	Not noted	Mucous membrane caked uniformly brown-red	As in stomach	None	None	Congested	None	Normal	Not noted	Large amounts free iodine in gastric contents
17	2 hours	Unknown	Not noted	Mucous membrane thick gray, parched, patchily blackened and eroded	Markedly congested	Mucous membrane of upper jejunum markedly congested	None	Fatty	None	Normal	"Normal"	Large amounts free iodine in gastric contents
18	7 hours	Unknown	Not noted	Normal	Mucous membrane stained brown; contains small amount of blood	None	None	Fatty	None	Normal	"Normal"	Iodide 24.4 mg. in gastric contents, 11.5 mg. in 1000 gm. liver tissue

lavage of the stomach with starch and milk had been performed early in the treatment.

In all but three instances the kidneys showed pallor, congestion, or indistinct markings. In two instances the cortex was noted as swollen, in one as indistinguishable from the medulla. Here again neither the amount of iodine ingested nor that found in the kidney nor the time interval between ingestion and death could be correlated with the gross anatomical findings. Histologic examination was done only in case 2, in which there was found intense congestion of the interstitial capillaries, and red cells and red cell casts in the collecting tubules. There was intense, but rather patchy, congestion of the glomerular capillaries; this contrasts with the findings in our own case in which the glomeruli were chiefly bloodless and their lumina apparently occluded by the swollen endothelial cells in apposition. This apparent morphological difference may be due to the difference in the length of life after the iodine ingestion. The longer duration in our case may have accounted for the reactive cellular changes observed in the glomeruli, the ischemia being due to the mechanical occlusion of the lumina by the swollen cells in apposition, a change obviously requiring more than the few hours interval present in case 2. In neither instance were there gross changes suggesting an acute diffuse glomerulo-nephritis or isolated glomerulitis nor was there histologically any increase in endothelial, epithelial or interstitial cells, no thickening of the basement membrane, nor any evidence of inflammation.

With material such as ours, dependent as it necessarily is on clinical reports from a number of institutions—which are never detailed and are frequently confined to a mere statement of the fact of iodine ingestion and its apparent intent—any analysis of symptoms is not entirely satisfactory. Nevertheless, anuria appears in the records twice (cases 1 and 9) and a clinical diagnosis of uremia once (case 9). These two cases are among those of longest duration in the series, respectively twelve and five days.

Because of the incompleteness of the data, an attempt was made to determine experimentally the effects of iodine on the kidneys. Two rabbits were given respectively 5 c.c. and 3 c.c. of tincture of iodine intravenously. The first rapidly went into shock and died in four hours. At autopsy no gross or histologic renal changes were apparent except for marked congestion of the glomerular and interstitial capillaries and a slight degree of cloudy swelling of the convoluted tubular epithelium. The liver showed moderate cloudy swelling, the cardiac muscle fibers were markedly swollen, the striations indistinct and markedly fragmented. The gastric mucosa was reddened but not eroded.

The second rabbit lived 24 hours. At autopsy, the renal, cardiac and hepatic findings, both grossly and microscopically, were identical with those noted in the first rabbit. The gastric mucosa of the pyloric half of the stomach showed a widespread ulceration and brownish discoloration of the

mucosa. The ulcer was shallow and covered by a friable, necrotic brownish membrane which, when separated, revealed the ulcer base formed by the reddened muscularis. Its edges were formed by reddened, edematous mucosa which was easily separable from the gastric wall. On section, the ulcer was covered by necrotic mucosa and a leukocytic debris. In the superficial layer of the muscularis were thrombosed veins with necrotic walls. Chemical examination of the gastric contents revealed iodine in organic combination.

Two other fasting rabbits were given 5 c.c. of tincture of iodine by nasal catheter (under fluoroscopic guidance) intragastrically. These exhibited no untoward symptoms and lived for one week and 10 days respectively. At autopsy, mucosal necrosis of the gastric fundus near the pylorus was noted in each rabbit as well as of the adjacent duodenum. No gross or histologic renal changes were present. The liver showed marked and widespread fat phanerotic changes, involving the greater part of each lobule. The heart muscle showed considerable cloudy swelling. The urea nitrogen had risen from 16 mg. per cent to 41 mg. per cent before death.

Because of the presence of only moderate congestive glomerular findings, both in the human cases and in the experimental animals, it is doubtful whether the apparent uremia was of renal origin. In most cases of iodine ingestion, severe and protracted vomiting or gastric lavages, often repeated, result in the loss of large quantities of electrolytes. It is doubtful if any electrolytes taken in solution orally can be absorbed through a mucosa so congested, baked, caked, necrotic, or ulcerated as that usually seen in the stomach and adjacent duodenum and occasionally in the small intestines in cases of iodine ingestion. Even in those cases where no gross mucosal involvement is present, the intestines are usually dilated and contain large amount of grumous, gray, turbid, or blackened material. These findings resemble those present in paralytic ileus. There is no question but what serious loss of electrolytes and water will cause renal suppression with a resulting nitrogen retention, a condition long recognized and treated in cases of intestinal obstruction. It is further a matter of everyday clinical experience that such a state occurs more rapidly the higher the obstruction. In cases of iodine poisoning the pathologic changes are usually in the stomach, duodenum and upper intestine.

It has also been shown that urinary suppression and a rise in blood nitrogen can be produced by forced diuresis initiated by repeated injections of sucrose.[12] It is possible that glucose acts in a similar manner.[18] Yet, in an attempt to spare the liver from damage so frequently present in the cases cited, the intravenous injection of glucose was resorted to in our case, as is usual in clinical practice. However, as we have here shown, the kidneys in cases of iodine poisoning already show cloudy swelling and probably increased permeability. It can therefore easily be seen how this procedure only increases the dehydration thus further increasing the toxemia. It

would be better merely to replace electrolytes by the intravenous route and leave until later in the clinical course the administration of caloric necessities and then by the subcutaneous rather than the intravenous routes. It may even be that the electrolytes and fluids themselves had better be administered subcutaneously as was done by Lejbowitsch.[4]

Of passing interest is the symptom of shock present in 11 of our cases (numbers 1, 2, 4, 5, 10, 12, 13, 15, 16, 17, 18). This may perhaps be associated with the myocardial changes such as were present in our experimental rabbits which were injected intravenously; or this shock may be due to a severe disturbance of the splanchnic nerves due to changes incident to the gastric and duodenal and hepatic lesions.[14]

Of interest also is the extremely early development of clinical symptoms and signs of pulmonary parenchymal (pneumonic) involvement, and the pathologic changes even a few hours after the ingestion of the drug. Thus, in case 2 dying about 10 hours after the iodine ingestion, " the trachea and larger bronchi contained a foul smelling, brown material and some yellow creamy pus pouring forth in large quantities from the upper and lower bronchi. The lungs, especially the lower lobes, are irregularly, but widely consolidated, the consolidation being distinctly peribronchial in distribution." In case 3 dying 13 hours after the iodine had been ingested, " the bronchi contained mushy gray purulent contents." It is possible that the gastric necrosis and the vomiting caused more than usual intrabronchial aspiration of gastric contents, and that lavage in the presence of such abnormal peristalsis and the marked relaxation of gastric and bronchial walls allowed of easy ingress of the lavage material into the lungs already the seat of an edema (case 1). No instances are recorded of the presence or absence of bacteria in the gastric contents but it is doubtful whether the ingested tincture of iodine can so rapidly eliminate organisms contained in the stomach.

Case 6 deserves brief individual comment. In this case there was a definite history of the ingestion of iodine with suicidal intent, and the presence of iodine burns of the lips and tongue. With gastric lavage the patient recovered from the acute symptoms, but thereafter gradually but progressively developed symptoms of esophageal obstruction. Esophagoscopy 33 days after the iodine ingestion revealed the mucous membrane just above the cardia to be so scarred as to cause stenosis. After two unsuccessful attempts at dilatation, gastrostomy was performed, the patient dying of a general peritonitis and mediastinitis four days thereafter. At autopsy a transverse puckering of the esophageal mucosa and scarring of the wall were present 3 cm. above the cardiac end of the stomach. The esophageal lumen was so narrowed that a probe 4 mm. in diameter could barely be passed into the stomach. The scarred area involved the entire terminal 3 cm. of esophagus and adjacent 2 cm. of gastric mucosa. The patient lived for 52 days after the ingestion of the drug and hence no chemical analysis for iodine was performed post mortem. However, the history

obtained repeatedly during the patient's lengthy stay in the hospital, as well as analysis of washings from the bottle supposed to have contained the drug ingested, failed utterly to indicate any substances other than iodine. So far as we could ascertain, this is the only recorded case of esophageal stenosis caused by iodine.

Case Report

On May 25, 1935, at about 1:30 p.m., a 29 year old white man was sent to the Beth-El Hospital by Dr. Nathan Davis four days after having taken an unknown amount of tincture of iodine during a period of despondency.

The patient appeared to be fairly well nourished but looked ill. His eyes reacted to light and accommodation; the sclerae were slightly jaundiced. No pathological changes were evident in the nose and throat. Examination of the mouth revealed dry lips and a dry coated tongue with a few ulcerations of the buccal mucosa. The breath presented a peculiar odor.

The expansion of the chest was fair. The respiratory rate was somewhat increased; no râles were heard. The heart was regular in rate and rhythm. The sounds were of good quality and no murmurs were heard. Examination of the abdomen showed some tenderness over the liver region. The rigid recti muscles prevented proper palpation of the liver and spleen. The skin was somewhat cyanotic but no jaundice was noted. The extremities showed no abnormal findings except a slight cyanosis under the nails.

The systolic blood pressure was 140, the diastolic 80, the pulse rate 96 per minute, respiration 24 per minute and the temperature 99.4° F.

On admission to the hospital, five ounces of urine were obtained by catheterization. It was smoky in color, specific gravity 1.010, acid in reaction, albumin 2 plus, glucose negative, and acetone positive; no casts were found; some white and red blood cells and epithelial cells were present. Iodine in organic combination was found in the urine. The blood count showed 5,000,000 red blood cells, 70 per cent hemoglobin, 14,000 white blood cells, with 85 per cent polymorphonuclear neutrophiles and 15 per cent lymphocytes. Blood chemistry: glucose 142 mg. per cent; urea nitrogen 150 mg. per cent; non-protein nitrogen 228 mg. per cent; creatinine 7.5 mg. per cent; uric acid 5.6 mg. per cent; chlorides 556 mg. per cent; phosphorus 3.5 mg. per cent.

On admission, 250 c.c. of 25 per cent glucose solution were given intravenously and a retention enema of 1000 c.c. of 15 per cent glucose solution and 5 per cent sodium bicarbonate was also given. To rule out a possible gastric perforation a roentgenogram of the abdomen was taken. No evidence of free gas in the abdomen was found. The left kidney appeared larger than the right. There was no evidence of radio-opaque substance in the renal regions.

The first evening after admission the patient vomited a small amount of light brown fluid with bloody mucus, and passed a dark brown liquid stool. That night the patient complained of abdominal soreness. At 11 p.m. the patient was taken to the operating room, 600 c.c. of blood were removed and 450 c.c. of blood were given by direct transfusion. The blood pressure, taken again at this time, was 142 systolic and 60 diastolic. During the remainder of the night, the patient slept very little because of frequent and severe abdominal cramps.

During the second day the patient again complained of severe abdominal pain which was relieved by morphine sulphate. The patient vomited only once during the day. Intravenous injections of 250 c.c. of 25 per cent glucose solution were given during the morning and evening. At midday a solution of 1000 c.c. of normal saline was administered by hypodermoclysis. During the second night, the patient was

restless because of the continued abdominal pain but slept at short intervals. At 11 p.m. another hypodermoclysis of 750 c.c. of normal saline solution was given.

On the third day the jaundice noted in the sclerae on admission had practically disappeared. The abdomen was more distended; some rigidity in the upper right quadrant was noted. Only three ounces of urine were obtained by catheterization. At this time 500 c.c. of blood were again removed and an equal amount of whole blood given by direct transfusion. The patient continued to be restless and slept only at intervals.

On the fourth day 10 c.c. of sodium thiosulphate solution were given intravenously. Anuria developed, colonic irrigations were given with no evident benefit. On the fourth and fifth days the patient continued to be restless but treatment was continued. The blood urea rose to 172 mg. per cent and blood creatinine to 12 mg. per cent. The blood CO_2 was 18 volumes per cent. Sodium bicarbonate in a 5 per cent solution was given intravenously. During the night of the fifth day, the patient became irrational, very noisy and restless. Twitching developed in various parts of the body.

On the sixth day the temperature rose to 104° F., the patient sweated profusely, was still irrational and toward noon sank into coma. General cyanosis developed and the patient died at 6 p.m.

The urine was always dark and smoky, and contained hyaline and granular casts, but no red cells were found on the third day after admission. The temperature on admission was 99.4° F. and rose on the third day to 103.2° F. fluctuating on the fourth and fifth days and at the close of the fifth day rose to 104.2° F. coming down at the time of death on the sixth day to 102° F.

Autopsy Report: The body is that of an adult male of about 30 years of age, 62 inches in height, slight in build, weighing about 120 pounds. The pupils are equal and in mid-dilatation. There are no external evidences of injury. On the buccal mucosa just within the lip line several small white ulcerations are present, pinhead to lentil in size. There is no other discoloration of the buccal mucosa, gums or tongue.

The head was not examined.

The thyroid gland is normal in size and shape and weighs 21 grams. On section the gland reveals a finely lobulated appearance and is of a pale brownish red color not unlike skeletal muscle. There is no lymphadenopathy. Nothing unusual is found in the pharyngeal mucosa.

Internally, the esophagus is covered by a thin, friable membrane of a yellowish brown color in its lower third. This membrane strips easily revealing a reddened submucosa. The upper portion of the esophagus is intact.

The pleural cavities contain a small amount of clear yellow fluid. The visceral pleura is reddened and dull but not covered by any exudate.

The lungs are voluminous, heavy, soggy and moderately firm. The firm areas tend to be patchy in arrangement with the intervening areas pale and fluffy. On section the smaller bronchi contain variable quantities of debris (gastric contents). Moderately firm areas varying in size from a lung lobule to a third of the lobe are present and are irregularly distributed throughout the lungs. These areas are drier than the surrounding parenchyma. A definite relationship to the bronchi or vessels is lacking. The cut surfaces ooze large quantities of frothy serosanguinous fluid. The larger bronchi and lower end of the trachea show a red and edematous mucosa but there are no ulcerations or discolorations.

The pericardial cavity contains a few c.c. of clear yellow fluid. The heart is normal in size, shape and configuration. The valves and orifices show no changes. The ventricular muscle is of a deep brownish red color and is unusually soft and flabby. There are no areas of fibrosis or softening. The coronary vessels are soft and pliable.

The peritoneal cavity contains about 1200 c.c. of clear yellow fluid. The loops of the small bowel are heavy with contained fluid. All peritoneal surfaces are smooth and glistening.

The entire mucosal surface of the stomach is covered with a dirty yellowish membrane which is more pronounced in broad longitudinal streaks (rugae). The membrane strips easily revealing an intensely edematous and congested submucosa. This membrane stops abruptly at the pylorus. The gastric wall is thickened by edema and congestion. There is no exudate on its peritoneal surface. There are no perforations. The duodenum is intensely congested and edematous and stains a deep yellowish brown, but lacks a definite membrane such as is seen in the stomach. The duodenal lesion involves the entire length of the duodenum and a similar but progressively less marked lesion is seen in the first 10 inches of the jejunum (figure 1).

FIG. 1. Photograph of fresh liver, stomach and gall-bladder from our own case. The stomach was opened along the greater curvature to show the mucosal surface. Note the widespread necrosis and diphtheritic gastritis at *A*, the necrosis of tops of rugae at *B*, also the relatively intact mucosa of the lesser curvature near the pylorus at *C*. *D* is the liver and *E* the gall-bladder.

The remainder of the small intestine shows distention of the small veins with occasional minute extravasations of blood in the subserosal tissue.

The gall-bladder is markedly distended by an opaque muddy brown liquid of low viscosity. The mucosa of the gall-bladder shows a patchy denudation with ragged edges of mucosa which project into the lumen. The cystic duct, common duct, and hepatic ducts show no changes. The ampulla of Vater is normal.

The capsule of the liver is smooth and glistening. On section the organ shows a nutmeg-like appearance due to a brownish yellow deposit in the periportal region.

The individual lobules are markedly swollen. The general cut surface has a pale yellowish appearance.

The pancreas shows normal lobulation.

The colon is normal. The mucosa and submucosa of the rectum are markedly edematous.

The spleen is large and soft, and weighs 300 grams. The edges and notches are rounded. On section the pulp is everted over the cut edges. The Malpighian bodies are large, hazy and tend to be confluent. The pulp is moderately soft but not diffluent.

The kidneys weigh 160 grams each. The capsules strip easily leaving a smooth surface. On section the cortex is markedly widened and bulges over the cut edges. The cortical markings are hazy. The glomeruli are prominent as pinhead red dots. The medullary markings especially at the cortico-medullary junction are moderately hazy. The pelves and ureters show no abnormalities.

The bladder mucosa is somewhat reddened and edematous. The verumontanum projects into the bladder as a long finger-like structure with a reddened and edematous bulbous ending.

The adrenals show no abnormal findings.

Microscopical Examination: Sections of lung show patchy areas of consolidation distributed throughout all lobes of the lungs with intervening areas of parenchyma showing no changes beyond congestion and intra-alveolar edema. The consolidated portions of the lungs show an intra-alveolar exudate consisting of polymorphonuclear cells, large mononuclear cells and red blood cells and serum. The amount of fibrin in the exudate is minimal. The small bronchioles show complete or partial desquamation of their lining epithelium, their lumens are filled with desquamated epithelial and polymorphonuclear cells. The larger bronchioles show desquamation of the lining epithelium with moderate congestion and leukocytic infiltration of the walls.

Sections of the heart show no changes in the pericardium, myocardium or endocardium. The aorta shows scattered numbers of large mononuclear and wandering cells in the intima. No other unusual changes are noted.

The acini of the thyroid are large, but few are cystic. They are lined by cuboidal epithelial cells and are filled with a fairly homogenous pink colloid material. Many of the acini are smaller in size and contain little or no colloid material. The supporting stroma is moderately increased in amount and contains occasional patchy collections of small round cells.

The liver cells contain numerous fine vacuoles evenly distributed in the cells throughout all parts of the lobules. The cells are not markedly swollen. There are no abnormal cellular infiltrations. The vacuoles are stained bright red with Sudan III, are not stained with nile-blue sulphate, osmic acid or by the Lorrain-Smith-Dietrich method (vacuoles are fatty acids).

There are no unusual changes in the parenchyma, islands of Langerhans or ducts of the pancreas.

The glomerular loops in the kidney are bloodless. There is, however, no increase in the number of nuclei. In a few glomeruli a slight amorphous intracapsular exudate is found. The cells lining the parietal layer of Bowman's capsule are swollen, occasionally desquamated and tend to be of cuboidal or of low columnar variety. The convoluted tubules show a marked granular cytoplasmic swelling of their lining cells with disintegration of the peripheral half of the cells so that the lumen appears to be markedly widened. Many of the tubules are filled with well preserved or partially disintegrated red blood cells and large quantities of amorphous pigment.

Sections of the spleen show a diffuse reticulum cell hyperplasia and a moderate congestion of the pulp accompanied by small patchy recent hemorrhages into the red pulp.

The stratified squamous epithelium of the esophagus is rigid and tends to break off from the supporting stroma. The superficial layers of epithelium are keratinized. There are no unusual changes in the mucosal layer. The submucosa is moderately edematous and shows in places small focal collections of round cells while immediately beneath the epithelium there is a patchy leukocytic infiltration.

The mucosa of the stomach is almost completely necrotic. Recognizable epithelial cells are present only at the base of the glands. The upper portions of the gastric mucosa are converted into an amorphous eosinophilic mass. The submucosa is intensely congested, edematous and shows numerous lymphatics crowded with polymorphonuclear cells and lymphocytes. The cellular infiltrate extends along the interstitial tissue and vessels through all layers of the stomach including the serosa.

The mucosa of the gall-bladder is edematous. The stroma is markedly infiltrated with polymorphonuclear leukocytes and some lymphocytes. The cellular infiltration extends deeply into the fibro-muscular layer. Occasional lymphatics in the fibroserous layer are distended with polymorphonuclear leukocytes.

Sections of the jejunum show necrotic changes in the mucosa with varying degrees of edema and round cell infiltration of the submucosa. The severity of the lesion decreases as the distance from the pylorus increases. Sections of large bowel show no unusual changes.

Sections of skin and subcutaneous tissue show no abnormal changes in the skin or its appendages.

Sections of testicle show all phases of normal spermatogenesis in the seminiferous tubules.

No degenerative changes or loss of the normal striation could be noted in sections of the skeletal muscle.

Chemical examination disclosed large quantities of iodine as inorganic iodine in the liver and kidneys and both as inorganic and organic iodine in the bile. In the bile, tests for iodine were positive only after separation from conjugated proteins.

Summary

1. A case of fatal iodine poisoning, with detailed autopsy findings, is reported. Eighteen other cases are reported from the records of the Medical Examiner's Office of New York City. The infrequency of fatal iodine poisoning is remarked, but it is suggested that the condition is more prevalent than is currently believed.

2. The renal suppression and nitrogen retention occurring during the course of iodine poisoning is discussed. It is suggested that this happening is the result of extrarenal loss of electrolytes and dehydration. No significant renal lesions were found in the human cases or in the animals experimented upon. It is suggested that therapy be aimed at the replacement of electrolytes and water during the acute phase, and that glucose injections or other measures leading to forced diuresis be avoided.

3. The early appearance of shock and aspirational pneumonia are stressed and the possible mechanism discussed.

4. An instance of esophageal scarring and stenosis is recorded, the only one of its kind in the literature.

The authors desire to express their thanks to Dr. Nathan Davis for the earlier clinical data of this case and also to Dr. Thomas Gonzales, Acting Chief Medical Examiner of the City of New York, for permission to report the 18 cases from the Medical Examiner's Office.

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THE GALACTOSE TOLERANCE TEST IN JAUNDICE; A CONSIDERATION OF THE EVIDENCE PERMITTING THE MEASUREMENT OF GALACTOSE UTILIZATION BY URINARY EXCRETION; SOME SOURCES FOR ERROR IN ITS INTERPRETATION; AND AN ADDITION IN ROUTINE TECHNIC *

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In 1931, in a paper on the study of the metabolism of galactose in the human subject, Shay, Schloss and Bell [1] concluded that this hexose was best suited for testing the carbohydrate function of the liver. In order for the urinary excretion of this sugar, orally administered, to act as a measure of hepatic carbohydrate function, they considered the following among the necessary conditions: (1) that there be no renal threshold for the excretion of galactose; (2) that galactose utilization remain unmodified by the activity of those endocrine glands known to affect glucose metabolism; (3) that galactose be practically unutilizable by all tissues other than the liver.

Because of the bearing that these facts have upon our thesis, it is essential to examine the more recent evidence which may lend support to the above.

Some investigators have questioned the use of a fixed dose of galactose for this test. We cannot subscribe to the opinion of Roe and Schwartzman [2] that it is necessary to employ a dose of sugar commensurate with body weight. Shay, Schloss and Bell [1] have demonstrated that the utilization of galactose is independent of age, weight, or sex. Harding and Grant [3] also prefer the fixed dose of 40 grams. Although a test amount of the sugar varying with the body weight or with the body surface may seem more logical and scientific, these authors believe that such a fluctuating dose will give no greater uniformity of results. This belief is supported by a comparison of the results of Harding and van Nostrand,[4] who used a fixed dose of 50 grams, with those of Roe and Schwartzman [5] who employed a regulated dose of 1 gram per kilogram of body weight. The urinary excretion of both groups will be seen to show large fluctuations. More recently R. K. Owen,[6] studying a group of 30 normal subjects (15 male, 15 female) between the ages of 20 and 70, found, after a uniform 40 gram dose, a urinary excretion whose variation and average were similar to those found in the normal group studied by Shay, Schloss and Bell.[1]

The improvement in the chemical methods for the measurement of small amounts of galactose in the blood has given rise to the feeling that the

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blood galactose curve may be a better measure of galactose utilization than urinary excretion. This would be true if a renal threshold for galactose could be demonstrated. However, the most convincing evidence is against the existence of such a threshold. Folin and Berglund [7] first furnished adequate evidence of its absence. They found that very small doses of galactose produced an increase of urinary reducing substances. Later Goldblatt,[8] studying the blood sugar after galactose administration, observed urinary excretion of galactose in the absence of any rise in blood sugar. Harding and Grant,[3] from studies on arterial blood galactose, were convinced that galactosuria can occur with very little rise in blood galactose.

In the absence of a kidney threshold, the blood level of this sugar, so far as the galactose tolerance test is concerned, is of academic interest only. None of the advocates of blood galactose estimations has thus far demonstrated that these are more significant than the measurement of the urinary excretion of this substance in the application of this test to the differential diagnosis of jaundice. We can, therefore, see no reason for converting a valuable laboratory test from a simple office procedure into one almost prohibitive for routine clinical use.

Any liver function test dependent upon the utilization of a sugar must of necessity take into consideration the possible conversion of the test substance in tissues other than the liver. In 1922, Mann and Magath,[9] while studying the ability of various sugars to combat the hypoglycemia following liver extirpation in the dog, found that injected galactose failed to give any appreciable result. In 1931, Shay, Schloss and Bell [1] demonstrated that in the human subject, after ingestion of galactose, the injection of amounts of insulin capable of producing hypoglycemic blood levels with marked symptoms of hypoglycemia, failed to modify materially the urinary excretion of galactose. Roe and Schwartzman [5] in 1932 recorded similar results from experiments on dogs.

Following the injection of adrenalin chloride after galactose administration, one of us (H. S.) [1] found a greater output of reducing substances in the urine than had occurred without the adrenalin. However, differential fermentation showed that the extra reducing substances were fermentable, the non-fermentable fraction remaining similar in amount to that excreted when no adrenalin had been used. Further support of the independence of galactose utilization of factors which definitely modify glucose metabolism is shown in the results of Wierzuchowski.[10] He found that the assimilation of galactose by dogs receiving a continuous injection of two grams of this sugar per kilo per hour over a 10 hour period was not affected by the type of previous food, by hunger, by adrenalin or by thyroxin.

Arcq [11] working with dogs and cats recorded that galactose, after either intravenous injection or oral administration, will augment hepatic glycogen but will fail to form muscle glycogen in spite of optimal conditions for its formation.

Laquer and Meyer [12] studying suspensions of muscle tissue found that dextrose and levulose were transformed almost quantitatively into lactic acid, while galactose was not converted at all, or in insignificant amounts only.

Griesbach [13] in muscle perfusion experiments with galactose obtained no evidence of utilization. Very recently Roe and Cowgill [14] failed to find any oxidation or conversion into glycogen of galactose in voluntary muscle tissue. They studied the galactose content of afferent and efferent blood in the leg in the dog following galactose administration.

Mann [15] recovered from the urine more than 80 per cent of intravenously injected galactose in the dehepatized dog and more recently Bollman, Mann and Power [16] have been unable to prevent the onset of hypoglycemic convulsions in the dehepatized animals with relatively large amounts of galactose. Roe, Gilman and Cowgill [17] in 1934, from studies of the effect of the ingestion of galactose upon the respiratory quotient of the normal and depancreatized dog, reported that galactose per se is not oxidized in the dog; that its normal metabolism is conversion to an intermediate (glycogen) which may break down to glucose—a conclusion identical with that recorded by Shay, Schloss and Bell [1] in their studies on the human subject in 1931.

Despite the findings of Sherif and Holmes [18] that the presence of galactose prolongs the period during which the mammalian nerve consumes oxygen, indications are that this hexose does not play an important rôle in nerve cell activity: galactose consumption by nervous tissue must be slight in view of the results obtained in depancreatized animals. Thus Kosterlitz and Wedler [19, 20] as well as Bollman and Mann [21] have recovered in the urine amounts of galactose practically equivalent to those administered to depancreatized dogs. The excretion was recovered partly as glucose and partly as galactose.

Roe and Cowgill,[14] by estimating the galactose contents of the blood samples removed simultaneously from the common carotid artery and from the internal jugular vein in dogs, after galactose administration, failed to obtain any evidence of the oxidation of galactose by nerve tissue.

In the clinical application of the galactose tolerance test certain facts, although previously published,[22, 23] must be reiterated. *This test can have no value if applied as a general liver function test. As an aid in the differential diagnosis of jaundice it is of incalcuable value.* In the latter it has its greatest usefulness if applied early in the course of the jaundice.

The vital character of the carbohydrate function of the liver demands a large reserve in this organ. The remarkable regenerative capacity of the liver helps restore such a reserve. Impaired carbohydrate tolerance, therefore, becomes manifest only in the presence of acute diffuse liver cell damage, or in chronic damage, when the reserve has been spent and regeneration has failed. When diffuse damage has occurred and repair sets in, the carbohydrate function of the liver appears to be restored with great rapidity even when very little other change is discernible.

The galactose tolerance test, therefore, should be the first laboratory procedure employed in the study of jaundice. It is far more essential as an aid in determining therapy to know the galactose tolerance than it is to determine the number of milligrams of bile pigment in the blood or the icterus index. Aside from the fact that the tolerance should be determined early in the course of the jaundice, it should be repeated in two to three days if the results obtained are borderline. By a borderline reading we mean an output a little below 3 grams in the five hours of the test period.

In our work we have adopted the 3 gram level of urinary excretion of galactose as the upper limit of normal in the five hours after a 40 gram dose of the sugar. This figure we believe represents an adequate margin of safety. We have seldom under such conditions seen a urinary output of more than 2 grams in the normal individual. Owen [6] has recently reported similar results. Readings between 2.5 and 3 grams, therefore, require a repetition of the test, in order to be able to interpret the results with certainty. Such readings usually occur in very mild forms of acute diffuse hepatitis, in which cases the readings may remain below 3 grams throughout the course of the disease. Then the short duration of the jaundice, the usually slight jaundice, as well as a rapidly diminishing galactose output to definitely normal levels on repeated testing, will indicate the mildness of the affection. Schiff and Senior [24] have recently reported such a case.

In other instances the carbohydrate function will be sufficiently disturbed to give a positive galactose test for only a short time and then will quickly return to normal as recovery rapidly sets in. Such cases indicate the importance of utilizing this test early in the course of jaundice. This point is illustrated by the following case.

J. F., aged 52, had been in excellent health until a week before admission when nausea appeared. About the same time jaundice was first noticed. There was no pain. A galactose tolerance test on the day of admission gave a reading of 3.46 grams; two days later a repetition of the test gave an output of only 2 grams; and three subsequent tests were all below 2 grams in spite of the fact that the blood bilirubin decreased very slowly.

Had the galactose tolerance test been delayed for two days, this case would have been classified under the failures for the test. The subsequent course and history indicated that we were dealing with a hepato-cellular jaundice which had had only a short period of disturbed carbohydrate function.

It is certainly no indictment of the test if it is found negative when applied first in the third or fourth week of a toxic hepatitis, at which time liver regeneration and repair in many instances will have been sufficient for the restoration of the vital carbohydrate function. Nor does it seriously impair the value of the test if it is found positive occasionally in an obstructive jaundice of several weeks' duration. By this time the reserve of the liver may have been overtaxed or the jaundice may have become associated with infection of the biliary tree which has had time to spread and

superimpose diffuse hepatic cell damage upon the initial obstruction. We believe that the few unfavorable reports on the galactose tolerance test in jaundice have been due to the failure to apply strictly the criteria which we have stressed in the interpretation of results and to a lack of consideration of the limiting factors imposed by the peculiarity of the liver itself, and not to a weakness of the test itself. All these difficulties can be avoided if the test is applied early in the course of the jaundice. The recent reports of Schiff and Senior, of Rosenberg [25] and of Tumen and Piersol [26] confirm this opinion.

A recent experience has indicated a possible explanation for some false positive results. As previously stated the metabolism of galactose is in all likelihood a conversion first to glycogen and then to blood glucose. Blanco,[27] Block and Weisz [28] and Harding and Grant [3] have clearly demonstrated that a rise in blood glucose may follow the administration of galactose. The conversion of galactose to glucose in the diabetic too is indicated by the increased blood glucose found by Roe and Schwartzman [5] after galactose ingestion. In normal rabbits, Roe and Cowgill [14] found that the fall in blood galactose over a four hour period following this sugar sometimes occurred concomitantly with a gradual steady increase in blood glucose. It appears that the rise in blood glucose following the ingestion of 40 grams of galactose may be sufficient to result in an excretion of glucose in the urine in some cases of impaired kidney tubule absorption (so-called low kidney threshold). That this mechanism may be responsible for a false positive galactose tolerance test is indicated by the following instance. M. G., aged 42, presented a history and other data which appeared to indicate a complete common duct obstruction by a stone, yet the galactose output was 3.4 grams. In the absence of long standing jaundice or marked infection in the biliary tree, it was difficult to reconcile the galactose tolerance with the other findings. After fermentation of the urine, however, it was found that the galactose fraction was not over 2.1 grams, the additional 1.3 grams having been present in the form of glucose. A glucose tolerance test done subsequently on this patient yielded strongly positive urinary reducing reactions even though the peak of the blood sugar curve reached only 148 mg. of glucose per 100 c.c. of blood. We have been thus prompted to add the differential fermentation as a routine in all cases in which the urinary excretion after 40 grams of galactose is over three grams. We now carry out the fermentation test as follows:

A suspension of yeast in water is centrifuged, and the supernatant liquid is discarded. Fresh water is added to the yeast, the two are again mixed, centrifuged and again the supernatant liquid is discarded. At the third washing, the supernatant liquid is tested qualitatively for reducing substances with Benedict's or Fehling's solution. If none is present, the yeast is ready for use. Three or more washings are generally necessary for the preparation. Portions of this packed yeast are then transferred to 50 c.c. of the urine sample, and to 25 c.c. of an approximately 1 per cent solution of glucose. The two are then incubated for 30 minutes at 37° C. and the concentration of sugar again determined. The fermentation of the glucose solution

is included as a control on the activity of the yeast. The concentration of reducing substances remaining in the fermented urine is taken as the measure of the galactose excreted.

SUMMARY

1. The galactose tolerance test may be carried out with a fixed dose of galactose, since the utilization of galactose appears to be independent of age, weight or sex.

2. Because the utilization of galactose by tissues other than the liver is minimal or nil, and because of the absence of a kidney threshold for galactose, the urinary excretion after a standard dose of galactose may be taken as a measure of the carbohydrate function of the liver.

3. The determination of the blood sugar curve after galactose is of no value in measuring the utilization of the sugar, because its conversion to glycogen by the liver may alter the glucose content of the blood during the test. The determination of the blood galactose curve greatly detracts from the value of the test by complicating the technical procedure while adding nothing to the accuracy of the results.

4. *In the clinical application of the test the time at which the test is performed in relation to the time of appearance of the jaundice is of utmost importance.* The test has its greatest value and the results are most reliable when it is performed soon after the appearance of the jaundice. The longer the duration of the jaundice before the test is done the more frequently will the results be misleading.

5. Very mild cases of hepato-cellular jaundice may give a negative galactose test throughout the course of the disease. The other clinical and laboratory data will serve to identify this group.

6. The test has its greatest value in the painless jaundice group of middle and later life. If used early and judiciously in this group it will be of immense help in prognosis and will help prevent unnecessary surgery in the hepato-cellular jaundice of those age periods.

7. Because of the possibility of some glucose excretion after the dose of galactose in some disturbed endocrine states [thyroid, adrenal, pituitary, potential or mild unrecognized diabetes, or in cases of impaired renal tubular absorption (so-called low renal threshold)], we feel that differential fermentation of the urine with properly prepared yeast should be made part of the routine technic in all cases in which the excretion of reducing substances in the five hour urine exceeds 3 grams.

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NIGHT BLINDNESS AS A CRITERION OF VITAMIN A DEFICIENCY: REVIEW OF THE LITERATURE WITH PRELIMINARY OBSERVATIONS OF THE DEGREE AND PREVALENCE OF VITAMIN A DEFICIENCY AMONG ADULTS IN BOTH HEALTH AND DISEASE *

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IN contrast to the hundreds of papers concerning the experimental, chemical, and pathological aspects of vitamin A deficiency are the small number of clinical studies. Such clinical investigations as are available deal, for the most part, with infants and children; and until recently, the manifestations of deficiency in adults have been overlooked or ignored.[1, 2, 3]

Probably few physicians in this country are aware that there are now available several methods of quantitatively estimating the degree of vitamin A deficiency in humans, and further that some of these methods are simple enough for routine clinical use. Investigations in Europe and this country have shown that our conception of the prevalence of avitaminosis must be revised. In this country, Jeans and Zentmire [4] and Sandler [5] have investigated the prevalence of vitamin A deficiency in children. However, there have been no studies on adults using this technic, except by Park,[6, 7] whose work has appeared since the inception of this investigation.

It is the purpose of this paper to report some observations concerning the degree and prevalence of vitamin A deficiency among a group of supposedly normal adults and also to give some preliminary results obtained by testing persons afflicted with various types of diseases. The important literature dealing with vitamin A deficiency will be briefly reviewed, since much of it is widely scattered and a proper orientation is necessary to understand the significance of the newer developments in this field.

PHYSIOLOGY AND BIOCHEMISTRY OF VITAMIN A

To truly appreciate the clinical manifestations of vitamin A deficiency, it is necessary to know where and in what form the vitamin is found, what happens to it after ingestion, where it is stored in the body and the rôle it plays in conditioning functional activities of humans.

The vitamin A content of our diet comes from two distinct sources, namely: alpha, beta, and gamma carotene and cryptoxanthin (grouped under the designation carotene or carotenoid substances for convenience) from the plant kingdom; and true vitamin A from certain animal tissues.[8]

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Animals and humans are unable to synthesize either carotene or vitamin A in their bodies and must depend on exogenous sources for their supply. The carotenoid substances are synthesized by plants, and from them the animals of both land and water derive their supplies either directly, or indirectly by preying on other animals.[9]

A recent editorial in the *Journal of the American Medical Association*[10] summarizes the differences between carotene and vitamin A as follows: "They are not identical substances: carotene is yellow, whereas vitamin A has little color; vitamin A exhibits an absorption of light of wave length 328 millimicrons, carotene does not, both give a blue color with antimony trichloride but that with vitamin A shows an absorption band of 619 millimicrons, whereas that with carotene absorbs light of wave length 590 millimicrons. Carotene is a crystallizable hydrocarbon with a cyclic structure, related to the terpenes, and the recent evidences indicate that vitamin A is probably a primary alcohol derivative of one half the carotene molecule."

Being fat soluble substances, both carotene and vitamin A are absorbed by the lacteals of the intestine, become intimately associated with the chyle and enter the general circulation through the thoracic duct.[11] No change in either substance takes place during the absorbing process. Vitamin A is directly stored in the liver until used by the body. Carotene is changed to vitamin A in the liver by an enzyme called carotenase, one molecule of carotene giving rise to two molecules of vitamin A.[12] The liver also plays an important part in the regulation of the concentration of the vitamin throughout the remainder of the body.[9] Examination of livers of healthy humans killed by accident, shows that the vitamin A content tends to remain constant within certain limits.[13] However, when the diet was poor the amount of this vitamin stored in the liver was found to be less than normal.

Rowntree[14] was able to show that even after the ingestion of an excess of the vitamin only 2 to 12 per cent was lost in the feces. Green[15] believes that the urinary excretion does not account for any significant loss and that if taken in excess, the unstored portion of the vitamin is destroyed in the liver or oxidized in the blood stream.

When this vitamin is entirely absent from the diet, experimental work suggests that it takes several weeks or longer to deplete the liver store and cause vitamin A deficiency to become manifest clinically.[9]

Fever,[8] rapid growth,[16] general infection,[17] elevated basal metabolic rate,[18] and pregnancy[19] all increase the metabolic need for vitamin A. Lack of bile[20] or pancreatic secretion,[21] changes in the gastrointestinal mucosa,[7] and disturbances of motility of the gastrointestinal tract[17] all prevent or hinder the proper absorption of this vitamin. Liver disease[17] prevents the proper storage of vitamin A as well as the conversion of carotene to vitamin A. Any of these mechanisms can lead to vitamin A deficiency even though the amount of the vitamin in the diet is theoretically adequate.

Both carotene and vitamin A are effective when given parenterally.[9]

The functions of vitamin A have not been entirely settled. Its growth promoting and anti xerophthalmic functions are well established.[9] Mendel[9] is not sure whether it is a necessary integral part of structures like the epithelial cells or whether it acts as a catalyst or as a " regulator " of certain cellular functions. The anti-infective nature of this vitamin has been the subject of much controversy. The most reasonable stand is taken by Mendel[9] who believes: ". . . that its influence is felt indirectly in that the vitamin helps to preserve the physiologic integrity of various epithelial structures and thus to maintain the 'first line of defense' against the invasion of bacteria."

It seems to matter little whether the vitamin is present as pure vitamin A or carotene in our food. Cow's milk, human milk, eggs, animal livers, cod-liver oil and cheese all contain adequate amounts of vitamin A. Butter contains both vitamin A and carotene. Spinach, watercress, carrots, green peas, lettuce, oranges and tomatoes are among the better sources of carotene. Storage, bleaching, oxidation and other processes may reduce the vitamin activity of any food.[5]

Pathology of Vitamin A Deficiency

Eusterman and Wilbur[22] in their review wisely suggest that a broad view of the pathology of vitamin A deficiency be taken and that attention be not, as in the past, concentrated chiefly on changes in the ocular organs. Wolbach and Howe,[23, 24] Goldblatt and Benischek[25] and many others have shown by experimental studies that specific changes in the tissues in vitamin A deficiency affect primarily the epithelial tissues, and consist of substitution of keratinized stratified squamous epithelium for normal columnar epithelium. Such changes were found in the eyes, para ocular glands, genito-urinary tract, alimentary tract and respiratory tract. Emaciation and atrophy of glandular organs were occasionally found. There is at present question whether or not the central nervous system is involved.[26]

Pathologic studies of avitaminosis A in human beings, although few in number, have been considered to show lesions identical with those found in experimental rats.[21, 27, 28] This aspect of the subject has been reviewed recently by Blackfan and Wolbach[21] and Sweet and K'Ang.[2] To the basic animal work have recently been added the histological studies of the skin lesions in humans.[29]

Since intact, healthy epithelial membranes, which constitute the first line of defense against bacterial invasion, are destroyed by vitamin A deficiency, secondary infection commonly complicates the more advanced cases and is the cause of most of the deaths.[2]

Blackfan and Wolbach,[21] in studying humans, were able to show at postmortem examination that often various tissues showed microscopic evidence of vitamin A deficiency even though grossly the organs appeared

normal and during life the patient presented no gross clinical evidence of vitamin deficiency. Since they studied small children or infants, it was impossible to state whether or not hemeralopia existed during life.

These observations are important in that they suggest that mild degrees of vitamin A deficiency (such as can be detected by the photometer) may be associated with microscopic changes in various epithelial tissues throughout the body.

Clinical Picture of Vitamin A Deficiency

It is generally accepted now that in adults and older children, essential hemeralopia (night blindness) is almost always the earliest manifestation of vitamin A deficiency.[1, 2] In infants and small children this symptom is of course easily overlooked. In contrast to infants, where the disease progresses rapidly, hemeralopia may for many years be the only manifestation in adults.[1, 30] It is also accepted that even severe degrees of hemeralopia can exist without ophthalmoscopically demonstrable changes in the eye being present.[1, 31]

As the degree of avitaminosis A progresses gross anatomical changes occur in the eye. Pillat [32] considers dryness of the conjunctiva (xerosis) to be the usual second stage of this disease. Both bulbar and palpebral conjunctivae may be dry and lustreless and contain spots (Bitot's spots) which have the appearance of foam or frost on a window pane. In size the spots may vary from tiny specks to areas large enough to cover the whole scleral area beyond the cornea. They are firmly attached to the conjunctiva and wrinkle peculiarly as the eye-ball is moved. There is lessened secretion of tears due to the inactivity of the para-ocular glands. The process at this stage is reversible under proper therapy. Excellent illustrations of Bitot's spots can be found in the papers by Spence [30] and Pillat.[33]

Keratomalacia is the last stage of the eye manifestations in adults as well as in infants.[32] This condition results from corneal softening which allows secondary infection to take place, and often leads to destruction of the eye and blindness. Pigmentation of the conjunctivae, giving the appearance of argyrosis, has been noticed, particularly in the dark skinned races.[33, 34] Meibomitis, blepharitis, hordeolum and edema and puffiness of the eyelids are common.[33] Insensibility of the cornea, almost to complete anesthesia, is frequent.[35]

By the time the second or xerotic stage in the eye is reached, other manifestations of avitaminosis A are noticed elsewhere in the body. This is, of course, in keeping with the pathological demonstration of widespread metaplasia of epithelial tissues.

Bronchopneumonia, bronchitis, bronchiectasis, infections of the nose and accessory sinuses or hoarseness are commonly seen when xerosis or keratomalacia is present, and indeed one of these complications (especially bronchopneumonia) is a common cause of death in vitamin A deficiency.

Probably next to the eyes, the skin undergoes the most marked and extensive change of all.[2] Dryness is the most frequent, but least characteristic change. Itching may occur. The most specific cutaneous lesion was described by Frazier and Hu,[29] and since repeatedly confirmed.[36, 37] The lesions vary from a slight roughening of the skin to papular cornified lesions surrounding the hair follicles, and are usually more marked over the extensor surfaces of the extremities and over the shoulders. The dry skin results from the deficient function of the sebaceous and sweat glands. Numerous comedones on the face are frequent. Hair may become dry, coarse and brittle, and fall out. In infants and small children the skin manifestations are limited to dryness, scaliness and shriveling, and only rarely show the keratinized plugs in the hair follicles. Frazier [29] and Mackay [38] believe that skin lesions may exist before xerosis is present and are a valuable sign of avitaminosis A when the presence of hemeralopia cannot be ascertained (as in children or when a photometer is not available for testing adults).

Loss of weight, weakness, genito-urinary infections,[2] diarrhea [2] and mild anemia [39] are less frequent and less characteristic manifestations. The relationship in humans between the lack of vitamin A and the formation of kidney stones is still controversial,[40] as is that between avitaminosis A and the common cold.[41] Laboratory studies yield variable results.[2] A temperature of 101° to 104° F. (aside from that due to infection) may be present in the second and third stages in adults, and disappears in a few days under therapy.[33] A detailed discussion of the clinical picture can be found in the papers by Eusterman and Wilbur,[22] Blackfan and Wolbach,[21] Sweet [2] and Mackay.[38]

It should be appreciated that manifestations of avitaminosis A (other than hemeralopia), while rare in this country, continue to be the subject of periodic reports.[42, 43, 44, 45] If hemeralopia were searched for, probably most cases of vitamin A deficiency could be diagnosed before any gross changes had taken place.

Night Blindness

Night blindness, often called hemeralopia, dysaptatio visualis,[46] hesperanopia (French),[82] nyctanopia,[82] nutritional dyskotopia [47, 48] or erroneously nyctalopia, is the difficulty, and occasionally, inability to adapt the faculty of vision to very faint illumination.

There has been in the past considerable confusion as to the nomenclature of day blindness and night blindness. The terms hemeralopia (literally meaning day sight) and nyctalopia (meaning night sight) have been used interchangeably so often that the best usage of these terms is difficult to decide. Most modern authors and the "Quarterly Cumulative Index Medicus" list night blindness as hemeralopia. Edmund [46] suggests that the term nyctalopia, be used to designate the condition of being more easily dazzled by light than normally and hemeralopia be used to indicate a reduction of visual function in reduced illumination.

Hemeralopia (night blindness) may develop in many conditions causing changes either in the light-refractive apparatus of the eye or in the light-perceptive apparatus.[1] The first group is made up by affections of the cornea, anterior chamber, lens or vitreous humour. Conditions which can cause changes in the light-perceptive apparatus and cause hemeralopia include: retinitis, choroiditis, retinitis pigmentosa, detachment of the retina, optic atrophy, optic neuritis, sympathetic ophthalmia, glaucoma, excessive myopia, poisoning (quinine, carbon disulphid, various war gases, etc.) and Oguthis' disease.

Grouped under changes in the light-perceptive apparatus is essential or idiopathic hemeralopia due to vitamin A deficiency. *In this type of hemeralopia, however, there are no ophthalmoscopically demonstrable changes in the eye.*

There is now abundant evidence available to show that in older children and adults, essential hemeralopia is usually the earliest and the most constant manifestation of avitaminosis A,[1, 2] and that it may exist for years without any other sign of the deficiency appearing.[30] Only severe degrees of night blindness annoy the patient sufficiently to cause him to seek medical attention.[6] In this country, such cases are fairly uncommon as compared to the milder to moderate forms of hemeralopia which can be detected only by the methods to be described.[7] It is only beginning to be appreciated that a mild to moderate degree of night blindness may be present and interfere with the efficacy of dark adaptation and visual acuity in dim illumination without the person being aware of its existence.[1]

According to the duplicity theory of vision, the eye has two distinct mechanisms for sight. Photopic vision occurs only with light of moderate or high intensity and is essentially a function of the cones. With this type of vision objects are seen in their true color. Vision under faint illumination (scotopic vision) is mostly peripheral and primarily a function of the rods. If a spectrum of low intensity is viewed with the dark adapted eye it appears as a gray band differing in brightness in different parts. In other words, with dim vision objects are only seen as different intensities of gray. Rod function (scotopic vision) depends upon the metabolism of the phototrophic substance known as visual purple (rhodospin) of the retinal rod cells. Since, as it will be shown later, visual purple is formed from vitamin A, it follows that scotopic vision is intimately associated with the available supply of this vitamin. Practically all tests commonly performed on eyes (i.e. visual acuity, depth perception, accommodation, test for color blindness and ocular muscle balance) are conducted in good illumination and therefore depend on cone function. Since cone function does not depend upon a supply of visual purple or vitamin A, we can appreciate how a person may rate 100 per cent in all these tests and still be so night blind as to scarcely be able to get about in dim illumination. Also since none of these tests will detect night blindness, we can appreciate why mild degrees of this condition were readily overlooked in the past. It explains in addition why the special

tests to be discussed later must be utilized in testing for night blindness. It is well known that animals or birds lacking in cones can see only at night (rod vision) and those lacking in rods can see only in bright daylight (cone vision). In the human eye the rods are more numerous at the periphery and sparse about the fovea. This explains why scotopic vision is mostly peripheral. The periphery of the retina is sixty times as sensitive to light as the central parts. The cones on the other hand are more numerous about the fovea and diminish as the periphery is reached. Therefore photopic vision is more acute in the central portion of the eye.[49]

Visual purple (rhodospin) is very sensitive and becomes bleached and inactive when exposed to light (sunlight or artificial light) and rapidly regenerated if an adequate supply of vitamin A is present in the body. The chemical change which takes place during this bleaching of visual purple gives rise in the rods to impulses which are carried by the optic nerve to the brain and result in the registration of sight in terms of light and darkness.

Vitamin A has been shown to be the precursor of visual purple [50, 51] and the vitamin is present in large amounts in the retina.[52, 53] A deficient intake of this vitamin causes the body stores to be low and this in turn leads to slow and poor regeneration of visual purple. An inadequate supply of regenerated visual purple causes the retinal rod cells to be less sensitive to light, and this in turn causes poor vision under faint illumination (hemeralopia).

Wald [52, 54, 55] has done much to clarify the relationship between visual purple and vitamin A, and was able on frogs to work out the following cycle of vitamin A in the eye.

Vitamin A, by means of a thermal reaction, is changed to visual purple which is a conjugated protein. Exposure of visual purple to light causes the purple color to disappear and allows the yellow or orange colors due to retinene (visual yellow) to appear. Visual purple is synthesized in the retina, either by reversion from visual yellow (retinene) or by regeneration from a fresh supply of vitamin A. During this cycle, a certain amount of these substances is lost, necessitating the arrival of a constant supply of vitamin A in the blood stream.

Night blindness (hemeralopia), as a symptom, has been known since the time of the ancient Egyptians and Hippocrates.[2] Even the beneficial results of liver therapy were described by Paul of Aeginta.[56] Hemeralopia of a marked degree has been described repeatedly in the literature as occurring in prisoners, inmates of asylums, soldiers in barracks, in religious groups during fasts; in crews of vessels on long voyages, in starving people during famines or long sieges.[1] What was described by the old sailors as moon blindness was undoubtedly night blindness [56] and the older literature suggests it was as common as scurvy. During the World War, hemeralopia was very common in the soldiers of the Central European Armies, often rendering large groups unfit for night duty.[1, 57, 58]

It has been shown, in experimental animals [51] as well as in humans,[31] that hemeralopia becomes much more manifest in vitamin A deficiency after the eye has been exposed to light. A person who remained in a dimly lighted room all day would need but little visual purple to carry on his visual needs, as compared to a person who remained in the sunlight all day. Aykroyd [31] reports that on the Labrador coast, night blindness was common and severe in those fishermen who were outdoors all day in open boats and either much rarer or milder in those persons who remained indoors and worked at other trades, in spite of the fact that all persons ate the same type of food. Evidence was also presented which showed that no amount of exposure to sunlight could cause hemeralopia to appear if the diet contained a normal supply of vitamin A. Aykroyd [31] found further that it was the custom among some persons in Newfoundland and Labrador, where severe vitamin A deficiency was common, to wear a bandage over one eye while the other eye was left uncovered in order to see to carry on the day's activities. After dark they would remove the bandage. The eye which had been exposed to the sunlight would be night blind, but the other eye, which had been covered, would not be so severely affected and served them for sight until the next morning, when the procedure was again repeated. Wearing dark glasses during the daytime also helped persons with night blindness to have better visual acuity after dark.

As will be shown later, mild to moderate (and occasionally severe) degrees of hemeralopia due to vitamin A deficiency are fairly common among many supposedly healthy adults, both in this country and in Europe. An important conclusion to these studies is that this large group of individuals, without in most cases being aware of it, have vision which while normal in daytime, is inefficient in dim illumination. The degree of this inefficiency would vary, of course, directly with the degree of vitamin A deficiency which was present.

Certain important practical problems dealing with essential hemeralopia in persons who drive automobiles at night, aviators and workers in certain trades, have been discussed in detail elsewhere by Jeghers.[59] Chief among these has been the effect of minor and mild degrees of hemeralopia upon the skill of a person who drives an automobile at night.

Several persons were found who had night blindness severe enough to cause them to complain of difficulty in driving at night for fear of accidents and of being easily dazzled by the lights of oncoming automobiles. Many mild hemeralopics were found who drove automobiles and were unaware of this lowered visual acuity for dim illumination. Where tried, therapy caused complete relief of these symptoms and improvement in the ability to drive at night. In night driving we have what amounts to a perfect experiment to bring out hemeralopic manifestations if vitamin A deficiency exists. The glare from the lights of each oncoming car depletes a fraction of the visual purple. If the person has avitaminosis A, regeneration is slower than normal and not complete at the time. Several hours of night driving could

easily decrease the skill of a vitamin A deficient person to the point where his chance of having an accident would be greatly increased. Being an individual affair, automobile driving at night does not enable one to compare directly his skill with that of a person with normal dark adaptation. Hence, many persons probably accept minor degrees of difficulty in night driving as the usual experience of all drivers.

Park,[6] Vignalon,[60] Rollet,[61] Wilbur and Eusterman,[17] and Tilderquist[62] have all reported instances of hemeralopics who had accidents or marked difficulty in driving automobiles at night, and where vitamin A therapy was tried, all obtained relief. Mason's[63] survey shows that in this country a test for essential hemeralopia is not at present required of any candidate for a driver's license.

As defined by Edmund,[46] nyctalopia signifies the condition of being more easily dazzled by light than normally. In other words, a person with nyctalopia complains of being dazzled by an illumination which has no dazzling effect upon normal persons. While nyctalopia can be due to various eye diseases, Edmund has shown that it is present in many persons with hemeralopia and vitamin A deficiency, and that it will disappear after vitamin therapy. What is commonly known among autoists as "glare blindness" due to exposure to bright lights while driving at night, may be a manifestation of vitamin A deficiency in an as yet undetermined percentage of the cases. An extensive survey of the incidence of hemeralopia and "glare blindness" among automobile drivers is at present under way and will be reported upon later.

It has been amply demonstrated that normal visual acuity, as usually tested, is no guarantee against the presence of night blindness. Frandsen[3] had many hemeralopics with 20/20 day vision who had very poor vision in dim illumination. Likewise, it has been shown that mild to moderate degrees of hemeralopia are accepted as the normal situation, unless skill in performing an act in diminished illumination is compared to the simultaneous performance of a similar act by a person with normal dark adaptation.[59] For instance, a person with mild vitamin A deficiency will have more difficulty in going from bright daylight into a darkened cinema and find his way to a seat than will a person with a normal supply of vitamin A.

Methods of Detecting Vitamin A Deficiency

In the past, vitamin A deficiency was not recognized until marked hemeralopia, xerophthalmia or keratomalacia developed. It should again be emphasized that these manifestations represent severe and well advanced degrees of avitaminosis A, and are rare compared to the milder, and often clinically undetectable, degrees of deficiency.

For many years, foreign investigators have been using various types of photometers to measure quantitatively minor to moderate degrees of night blindness.[1, 57] It was also discovered empirically that hemeralopia not due

to intra-ocular disease would respond to food rich in vitamin A, with a subsidence of the symptoms and a return of the photometer reading to normal.[57, 58] The experimental demonstration by Fridericia and Holm[50] and Tansley[51] that vitamin A was necessary for regeneration of visual purple; the studies by Holm[64] by means of a jumping test conducted in a dimly lighted room, that hemeralopia was the first manifestation of vitamin A deficiency in rats; along with the numerous clinical studies showing the relationship between marked hemeralopia, *xerosis conjunctivae* and keratomalacia, and avitaminosis A[65, 66, 67] led to the logical conclusion that such photometer tests could be used to detect sub-clinical degrees of vitamin A deficiency.

In a recent monograph on the subject, Frandsen[1] summarizes the objective data concerning essential hemeralopia as follows: "These patients show an *increased minimum light visible*. In *reduced illumination* the acuity of vision is lowered, the field of vision for blue in higher degrees of hemeralopia becomes smaller than the field for red. Dark scotoma appears at higher clarity than in the case of normal light sense, the adaptation time is prolonged, the power of distinction is lowered—all signs which signify that the range of adaptation is reduced."

One of the following methods listed by Edmund[68] and Frandsen[1] can be used.

Method One:

Minimum light visible determination (faintest light which the eye can detect) sometimes together with plotting of adaptation curves.

Method Two:

Visual field examination at reduced illumination.

Method Three:

Visual acuity determinations at reduced illumination.

Method Four:

Examination of distinction power.

I. The first method involves the use of a photometer. Although various types of photometers can be used,[1, 68] the Birch-Hirschfeld photometer, introduced by Birch-Hirschfeld in 1916,[57] has been used for clinical studies in Europe,[1] China[69] and in the United States[4, 5, 6] with good results. In 1934, Jeans and Zentmire introduced in this country the Birch-Hirschfeld photometer as a means of measuring minor degrees of vitamin A deficiency. The mechanism and use of this instrument are described later.

An American firm has recently perfected a new photometer called the "Bio-Photometer"* (see figure 1). Since it was designed primarily for routine clinical use it will undoubtedly displace many of the more cumbersome photometers now on the market. It operates on the principle of measuring the minimum light visible and has the advantages of greater

* The Bio-Photometer is manufactured by the Frober-Faybor Company, Cleveland, Ohio.

portability, compactness, and of measuring the minimal light intensity which the eye can see directly in milli-foot candles. This photometer can measure differences of one-millionth of a foot candle of light. This obviates the necessity of standardization of the instrument by the operator and allows readings obtained by one instrument to be compared directly to another. In addition, a standard source of bleach light is provided within the instrument.

Jeans et al.[83] have recently given their experience with this photometer and explain the technic of its use. Since readings can be made in a few

FIG. 1. The bio-photometer. This instrument is compact, made in portable models, contains a standard light within the instrument for bleaching visual purple and measures the minimal light visible directly in milli-foot candles. (Photograph courtesy of the Frober-Faybor Company, Cleveland, Ohio).

seconds, the adaptation curve in the dark can be plotted instead of merely depending on a reading at the beginning and end of the dark adaptation period, such as in the Birch-Hirschfeld technic. Jeans et al.[83] were able to show that the " Bio-Photometer " is more sensitive than the Birch-Hirschfeld and will pick out border line cases of deficiency missed by other methods.

II. Visual field determinations serve as the second method of detecting essential hemeralopia and are according to Edmund [68] accurate and satisfactory for experimental studies but too complicated for routine use. *It is important that the test be done under reduced illumination* and standard-

ized on subjects with no intraocular disease and ingesting an adequate supply of vitamin A, if one wishes to detect minor degrees of hemeralopia.

Kiang,[70] studying subjects in China by the perimeter method, found concentric contraction of the visual fields with the blue field smaller than the red. The contraction of the color field was proportional to the severity of the deficiency. Following vitamin A therapy, the visual fields returned to normal size while the blue field became larger than the red.

III. The third method, examination of visual acuity at lower illumination, has been employed by a great many authors and gives a good expres-

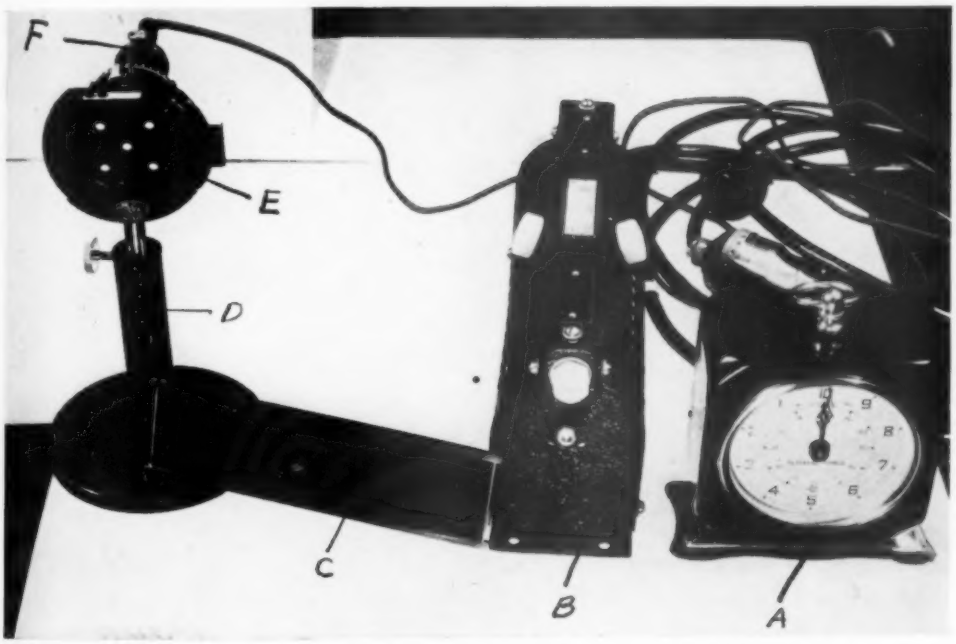

FIG. 2. Birch-Hirschfeld photometer used in experiments. (*a*) The time clock. (*b*) The rheostat for reducing current for photometer light. (*c*) The Goldberg wedge. (*d*) The Birch-Hirschfeld photometer. (*e*) The 5 point disc. (*f*) Handle which controls the aperture of the diaphragm. Directly behind (*f*) is the housing of the photometer light. The Goldberg wedge (*c*) slides into grooves before the 5 point disc (*e*).

sion of light sense of the eye, but is not a suitable method for routine clinical examination.[1]

IV. The fourth method, examination for distinction power, has been used extensively by Edmund,[3] Frandsen [1] and others in Denmark. This test requires the use of a set of eight Tscherning photometric glasses combined with Edmund's test charts. (See figure 3.) The photometric glasses are neutral-gray glasses, which absorb the passing light after a logarithmic scale, so that glass number 1 transmits 1/10 of the light, glass number 2—$1/10^2$, etc., to glass number 8 which transmits $1/10^8$ of the light. The test chart of Edmund consists of gray letters E of varying intensity on a white back-

ground. The distinction power is 0.00 when only the darkest letter can be seen, 0.25 if the next darkest E can be seen, etc., increasing by steps of 0.25 until a distinction power of 2.00 is needed to see the faintest letter.

The test is conducted by illuminating the test charts with a standard light (details can be found in the monograph by Edmund[3]). The darkest glasses (number 8) are placed before the subject's eyes. After complete

FIG. 3. Tacked on the upright board are the nine test charts devised by Edmunds. Each consists of the letter E, gray in color, on a pure white background. The darkest E measures a distinction power of 0.00, the next E measures a distinction power of 0.25, rising in steps of 0.25 until a distinction power of 2.00 is reached for the faintest E. The subject (facing the camera for illustrative purposes) is wearing a special pair of light-proof goggles into which the Tscherning photometric glasses fit. Two of the glasses are lying free on the table, along with an extra pair of goggles. The box on the table contains the complete graded set of Tscherning photometric glasses. The light which illuminates the letters is not shown. The fainter letters E are not visible on this photograph. During the test the subject reads the test charts at a distance of 25 to 50 centimeters.

adaptation in the dark, the subject is shown the illuminated charts. The faintest E which can be seen is the distinction power of the eye for illumination of glass number 8. The subject then closes his eyes and glasses number 7 are substituted for number 8 and the distinction power determined for glass number 7. This is repeated in turn for glasses number 6, 5, 4, 3, 2 and 1. The final reading is made without any glasses before the eyes. These values can be plotted on a graph (see figure 4). A typical normal

and also a curve from a vitamin A deficient person is shown. With vitamin therapy the deficient curve gradually approaches the normal curve. This method has the advantages of being independent of refractive errors, requires no training or intelligence on the part of the subject and the end point can be made objective by turning the E in various directions. The charts are read at a distance of 25 to 50 centimeters and a visual acuity of only 6/36 is needed to see them. This method of testing would be ideal

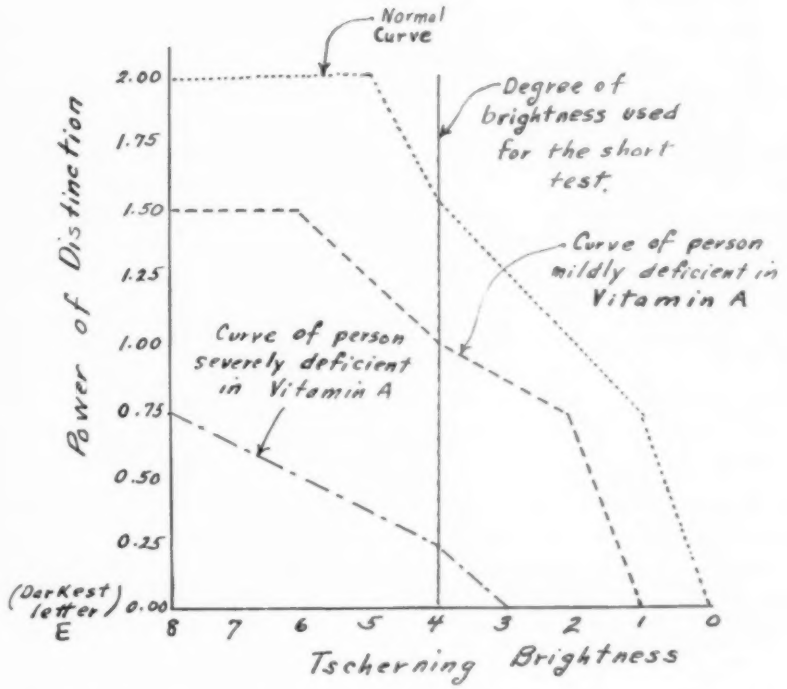

FIG. 4. Typical curves obtained when the power of distinction is plotted for different degrees of dim illumination. With proper vitamin A therapy the deficient curves gradually improve to coincide with the normal curve. The ability to see the darkest letter E is considered a power of distinction of 0.00. A distinction power of 2.00 is needed to see the faintest E. (Modified after Edmund.)

for aviators, because using this principle a test for spatial discrimination in dim illumination could be devised.

Edmund [3] has shown that the test can also be shortened by using only one determination, usually with the Tscherning photometric glass number 4. This test takes but a few minutes.

The writer is at present conducting an extensive study of vitamin A deficiency comparing Edmund's method and the Bio-Photometer. These results will be published later.

Prior to use of these tests for hemeralopia as a measure of vitamin A deficiency, other laboratory procedures were used for detecting mild degrees

of deficiency of this vitamin. Many workers [2, 21, 30] have suggested examining the urine, tracheal secretions, or scrapings from the nasal mucosa or conjunctivae. In any of these, the demonstration of cornified epithelial cells is considered presumptive evidence of avitaminosis A. While useful in the hands of experts, these methods are crude, positive in only the more advanced cases and non quantitative as compared to the visual procedures described.

Carr and Price [84] found that antimony trichloride produced a blue color with vitamin A. This test can be used to detect the amount of vitamin A present in the blood stream. Attempts are being made to develop this into a clinical test of vitamin A deficiency.[85] Further studies may prove this to be a valuable adjunct to study and diagnosis of vitamin A deficiency. It has been shown that the amount of vitamin A in the blood stream varies with the diet, age and infection. What is needed is a series of studies correlating the blood vitamin A and carotene with measurements of night blindness and response of each to proper therapy.

Unfortunately tests for vitamin A deficiency which depend upon some objective manifestation of hemeralopia cannot be satisfactorily used on children under the age of five, due to the lack of intelligent coöperation. This leaves an important group with no test for sub-clinical degrees of vitamin A deficiency.

Quite recently, there appeared the preliminary report of a method which promises to be applicable to this at present undiagnosable group. Friderichsen and Edmund [71] were able to work out a method of detecting minor degrees of vitamin A deficiency which is quantitative and could be used to test children even during the first two years of life.

This method depends upon determining the faintest light irritament (minimum reflexible) that is able to provoke an oculomotoric reflex. The magnitude of the required irritament was proved to be fairly constant in normal infants and to depend on the power of adaptation. In infants who are not adapted to darkness a stronger light irritament is required to provoke ocular reflexes than in children adapted to darkness. Measuring the magnitude of the light irritament required in infants who have had the opportunity of adapting themselves to darkness makes it possible to obtain a quantitative idea of the presence of hemeralopia and indirectly the degree of vitamin A deficiency. Follow up studies with this technic [88] have shown that vitamin A deficiency is common in infants. Rapid return to a normal minimum reflexible followed vitamin A therapy in those who had low readings.

Technic

The Birch-Hirschfeld photometer * was used in this study (figure 2). The technic of its use and working mechanism are described in detail in the papers by Birch-Hirschfeld [57] and Jeans and Zentmire.[4]

* The Birch-Hirschfeld Photometer was of Zeiss manufacture.

The instrument consists essentially of a metal tube with a light of constant illumination at one end and an iris diaphragm at the other end. This diaphragm allows the aperture to vary from two to 20 millimeters in 10 separate steps. A metal disc containing five holes punched out in the five point quincunx of the throw dice is placed before the diaphragm. In front of the disc slides a Goldberg wedge. This wedge is essentially a glass slide of 13 different opacities, ranging from complete transmission of light at the left end and zero transmission of light at the right end. Various combinations of the 10 diaphragmatic apertures and the 13 different degrees of opacities on the wedge give over 100 finely graduated steps of light intensity.

A light proof dark closet was prepared on each of two wards, with one wall painted white to facilitate bright illumination. The subject was seated facing the white wall in a position similar to that used by Jeans and Zentmire [4] with the eyes 60 centimeters from the photometer scale and 100 centimeters from the wall.

After exposure of the eyes for five minutes to the indirect light from a 200 watt electric bulb which shines on the white wall (to use up visual purple), the room was made completely dark and an initial reading was taken of the faintest light which the subject was able to see (minimum light visible).

The two holes on the left of the disc, the center hole and the two holes on the right side of the disc were each covered by a different opacity on the Goldberg wedge. In closing the diaphragm the holes on the right disappeared first, then the center hole and finally the left two holes. The point at which the right hand holes disappeared and the center and left hand holes were just visible was recorded as the end point. It is best to begin with a wedge opacity reading of three. If the light from the two millimeter aperture of the diaphragm can be seen as described above, then the wedge opacity is set at four, the diaphragm opened to 20 millimeters and reduced step by step. If, however, on the first wedge opacity tried, the light from the 20 millimeter aperture is not seen, a less opaque wedge setting is used and the process is repeated until the proper arrangement of the lights is finally read.

The eyes were then allowed to accommodate in total darkness for 10 minutes and the reading on the photometer repeated. As the visual purple regenerates fainter and fainter light intensities can be detected. The regeneration time period must be kept constant and timed with an alarm which rings a bell. It is important that during this period no lights of any kind be used in the room.

For this reason it is necessary to memorize the clicks as the wedge and diaphragm position are shifted so that the final reading can be obtained in complete darkness. This is readily accomplished after a short period of practice.

Each reading consists of the wedge position—varying from zero (no opacity) to 13 (complete opacity) and the iris diaphragm aperture varying from two millimeters to 20 millimeters in steps of two millimeters.

The entire procedure takes less than 20 minutes. The photometer, before being used, must be standardized on a group of healthy adults who have taken vitamin A concentrate for several weeks or have had an adequate diet for several months, as well as being free of any intra-ocular disease. In performing the test, a few subjects were troubled with "after images" and were not sure of the end point. This was particularly apt to happen if a long time was taken to reach the proper wedge opacity for the final aperture reading. Skill in handling the photometer and alert coöperation on the part of the subject will minimize this difficulty. Also covering the photometer scale for 10 to 20 seconds to rest the subject's eyes and repeating the reading usually enabled a satisfactory end point to be reached. Those persons who wore glasses were asked to do so during the test. However, this

is not absolutely necessary since Frandsen [1] was able to show that minor refractive errors played no part in causing hemeralopia.

It is important to be sure that no intra-ocular condition is present which can cause night blindness, before assigning the lowered photometer readings to vitamin A deficiency.

Edmund [3] and Frandsen [1] have shown that familiarity with this general method (by repeated trials) did not change the reading of distinction power obtained. In the present series, repeated tests at monthly intervals on several subjects and often by different operators gave essentially the same reading.

Results and Discussion

A total of 274 satisfactory photometer tests were performed. The results are summarized in table 1. The subjects were divided into three groups as follows:

Group I: Consisted of 22 physicians who ate in the doctors' dining room at the Boston City Hospital.

Group II: Consisted of 149 subjects comprising WPA employees, medical students, technicians and graduate nurses.

Group III: Consisted of 103 ambulatory patients. Tests in this group were usually made shortly before discharge.

Table I

Summary of 274 Photometer Tests for Vitamin A Deficiency

Group	Subject		Normal	Mild	Moderate	Severe	Total
Group One	House Officers	Number	20	2	0	0	22
		Percentage	91	9	0	0	
Group Two	WPA Workers Medical Students Technicians Graduate Nurses	Number	98	42	7	2	149
		Percentage	65.8	28.2	4.6	1.4	
Group Three	Ambulatory Patients	Number	34	43	18	8	103
		Percentage	33.0	41.7	17.6	7.7	

Because of the excellent coöperation, reliable dietary history and the uniform nature of their diet, the members of group one were considered the control group. They were all healthy males varying from 24 to 35 years of age and free of serious intra-ocular disease.

The meals served in the doctors' dining room contained a varied and abundant supply of both vitamin A and carotene. Butter, milk and cream, in unlimited amounts, were served at every meal, eggs five times per week, cheese once per week, liver once per week, whipped cream on desserts weekly,

ice cream three times weekly, and pigmented (yellow or green) vegetables and fruit daily and often at each meal. From a theoretical consideration such a diet supplies more than the minimum amount of the vitamin needed.

With two exceptions, the photometer reading of each person in this group fell into a narrow range which was considered as normal. Each initial reading (after the five minute exposure to bright light) varied from wedge opacity four with a diaphragm aperture of 10 millimeters or less to a wedge opacity of five with a diaphragm aperture of 10 to 20 millimeters. After the 10 minute dark adaptation period, all readings were from the opacity six of the wedge with a small diaphragm aperture up to a wedge opacity seven with a large diaphragm aperture.

Several subjects took carotene daily, in addition to their diet, with no change in the photometer reading. This is in agreement with the work of Frandsen [1] who found that larger supplies of vitamin A than the body needs did not improve the visual acuity for dim vision once it reached a normal level. Repeated tests on a few of the subjects by different operators gave essentially the same photometer readings.

The two doctors in this group who failed to have a normal photometer reading fell into the mildly deficient group. One was trying to reduce weight and had deliberately avoided foods rich in vitamin A. The other had many food dislikes which caused him to avoid certain foods rich in vitamin A.

It was decided that any reading through wedge opacity four or five at the initial reading, and through wedge opacity six or seven after the 10 minute period would be considered as falling into the normal range and that person to be free from vitamin A deficiency. Table 2 contains representative photometer readings of persons who were considered to be receiving an adequate supply of vitamin A in their diet. Mild deficiency was

TABLE II

Representative Photometer Readings Obtained on Persons Receiving an Adequate Supply of Vitamin A

Subject	Initial Reading		Ten Minute Reading	
	Wedge	Diaphragm	Wedge	Diaphragm
House Officer	5	16	6	8
House Officer	5	10	6	10
Student	4	6	6	6
Technician	4	8	6	6
Student	4	14	7	20
Student	4	10	6	10
House Officer	4	4	6	6
Patient	4	4	6	4
House Officer	4	8	7	18
Visiting Physician	4	8	6	10
WPA Worker	4	4	6	6
Nurse	5	14	6	4

considered to be present when the initial reading was through wedge opacity three and final 10 minute reading through wedge opacity five; and moderate deficiency when the initial reading was through wedge opacity two and the final reading through wedge opacity three or four. Severe deficiency was considered to be present if the wedge opacities readings were less than the moderately deficient group.

It should be appreciated at this point that moderate and severe deficiency by this classification does not mean that the person has xerophthalmia or keratomalacia, but that they represent different degrees of hemeralopia. *Those falling into the severe deficiency group (as classified on the basis of this photometer test) represent the instances of vitamin A deficiency which are on the borderline of being detected by the usual clinical signs and symptoms.*

Group two consisted of 149 subjects including WPA employees, medical students, technicians, and graduate nurses. All members of this group were healthy in the sense that they worked daily and had no specific complaints or diseases. Many of the WPA workers and medical students lived on surprisingly small incomes.

Compared to the control doctor group (with their adequate diet) the results here were entirely different, and probably representative of the general populace of poor financial circumstances.

Of 149 subjects tested, 98 (65.8 per cent) fell into the normal group (table 1). Of the rest, 42 (28.2 per cent) were mildly deficient in vitamin A; seven (4.6 per cent) moderately deficient; while two (1.4 per cent) were severely deficient.

Careful questioning of persons in the moderate or severe deficiency groups would often elicit complaints of some difficulty in vision in faint illumination. Several complained of difficulty in finding their way to a seat in a darkened cinema, trouble in driving an automobile at night or of being abnormally sensitive at night to glaring lights.

A study of the dietary habits of this group was interesting. The reasons for deficiency could usually be assigned to one of several obvious reasons. The financial reason was probably most important. A survey of the diet, consumed by control group one, which was shown to be adequate in vitamin A content, includes many expensive food substances. The best sources of vitamin A, such as butter, liver, cream, eggs, cheese and pigmented vegetables and fruits are distinctly expensive items. Persons who are forced to live on a frugal budget, whether they live at home or particularly if they eat in restaurants, can easily become deficient in vitamin A.

Peculiarities in food habits which cause foods rich in vitamin A or carotenoid substances to be avoided or disliked were responsible for several mild and moderate instances of deficiency. Another interesting group comprised those few persons (usually women) who because they feared obesity or were trying to reduce avoided many of the foods rich in vitamin A. The literature is replete with many papers emphasizing that a poorly

chosen reducing diet may cause any of several different deficiency syndromes. Vitamin A deficiency is no exception to this well known clinical observation. Such evidence indicates strongly the need for competent medical advice in the planning and supervision of any reducing regime.

Results secured by other workers, testing supposedly normal persons for vitamin A deficiency, can be compared to the results obtained in this group.

Jeans and Zentmire [72] tested 404 children, ages ranging from six to 15 years, selected at random at four different places throughout the state of Iowa. Evidence of vitamin A deficiency was found in 26 per cent of the rural group and 53 per cent of the village group. In an urban group the proportion of deficiency for the higher economic level was 56 per cent, for a middle level 63 per cent and for a low economic level 79 per cent. The low figure for the rural district can be accounted for by the abundance of dairy and vegetable products in the diet of the average farmer. Where tested, 95 per cent of the deficient persons had a return of the photometer reading to normal and disappearance of the deficiency, following oral ingestion of either vitamin A or carotene concentrates. Sandler [5] in studying a group of children living in an orphanage obtained results similar to the above.

Frandsen [1] and Edmund [3] have published extensive studies on this subject and have tested many hundreds of subjects, including both children and adults. These investigators found that the percentage of deficiency for vitamin A varied for each group tested. In one group, 65 per cent of apparently healthy school children from Copenhagen were found to show deficiency. Children from orphanages were deficient in an even greater percentage of cases. Of groups of adults tested, the percentage of deficiency varied considerably from low to very high figures, in one instance reaching 90 per cent. Diet and economic conditions were the important factors in determining the degree of deficiency.

Park [6, 7] in testing groups of adults for vitamin A deficiency by the photometer method found it to be present in percentages comparable to those obtained by Frandsen [1] and Jeans and Zentmire [72] for children. The rural group showed much less deficiency than the urban group. Women trying to reduce weight and persons who ate irregularly or improperly in restaurants were commonly found to be deficient. Park was able to cause the photometer reading to return to normal in practically every instance in a group of deficient persons who were given carotene orally.

These studies conducted in widely scattered locations (Denmark, Iowa, Chicago, Oklahoma and Boston) suggest the need for revision of our current conceptions of the prevalence of vitamin A deficiency which are based upon the old viewpoint, that marked hemeralopia, xerophthalmia or keratomalacia must be present before this diagnosis can be made. Hess and Kirby [73] in 1933, sent questionnaires to 50 leading ophthalmologists in this country and found that but few cases of severe night blindness or keratomalacia were observed. On the other hand evidence is accumulating to suggest that even clinically detectable night blindness is by no means rare if one carefully questions those persons whose photometer readings show marked impairment of dark adaptation. In the present series, several persons with such readings complained of difficulties referable to night blindness. Park [6] found 12 persons who complained of night blindness. One can conclude that clinically detectable vitamin A deficiency, while un-

common, is not as rare as formerly believed. However, the evidence already available indicates strongly that sub-clinical degrees of vitamin A deficiency are very common.

This raises the question of the adequacy of the average American diet in regard to the entire vitamin content. McLester,[74] in discussing general malnutrition, points out that man's diet is seldom faulty in respect to one factor alone. Editorially, the *Journal of the American Medical Association*[75] comments: "The physician is chiefly interested in nutritional failure not because of its relation to scurvy, beri beri or any other well defined disease, but because it produces numberless vague poorly defined states of ill health. To prevent nutritional failure, the diet should be considered as a whole, and all essentials, whether vitamin, protein or mineral, should be accorded equal importance."

A situation, entirely comparable to the sub-clinical type of vitamin A deficiency, exists in this country in regard to vitamin C deficiency. Dalldorf[76] remarks that, judged by clinical criteria, scurvy is uncommon in this country. An acquaintance with experimentally produced scurvy, however, indicates that various degrees of deficiency associated with a number of morbid changes can occur without classic symptoms or signs of the disease. Studies with the recently developed capillary fragility test[77] as a measure of sub-clinical scurvy and the direct determination of the amount of ascorbic acid in the blood plasma[78] suggest that sub-clinical degrees of scurvy are common.

Recent development of quantitative methods of determining other vitamin deficiencies has made the subject of sub-clinical deficiencies a practical and not a theoretical concept.[86, 87] That sub-clinical degrees of deficiency for any or all of the vitamins exists seems very likely. The entire subject seems worthy of much consideration, and the future may change our present concept of what constitutes an adequate diet for the American people.

Group three comprised 103 ambulatory patients convalescing from the usual run of diseases which one finds on a general medical ward. No very sick or bed-ridden patients were tested, because the subject had to be well enough to walk to the dark room, sit on a stool for 20 minutes and otherwise coöperate in the test. With about a dozen exceptions, the tests were performed shortly before discharge of the patient. Patients with liver and gastrointestinal diseases were tested on admission if they were able to walk to the dark room. An ophthalmoscopic examination was done on each of these patients and only those with normal fundi and clear cornea and lens were used. It was found that cataracts, glaucoma, corneal opacities and various types of retinitis caused low photometer readings.

Thirty-four (33 per cent) of those tested showed no deficiency. While group three is small, they represented, on the whole, those with less serious illnesses, often of short duration.

Forty-three (41.7 per cent) were found to be mildly deficient in vitamin

A; 18 (17.6 per cent) moderately deficient; and eight (7.7 per cent) severely deficient.

The sharp increase in the percentage of moderately and severely deficient persons in this group as compared to groups one and two can be explained as follows:

(1) The persons in this group belong for the most part in the lower economic level.

(2) Many had diseases which caused anorexia, vomiting, diarrhea or otherwise hindered the proper ingestion and absorption of the vitamin.

(3) Many were entirely ignorant of what constituted an adequate diet.

(4) Some had fever, infection or other disturbance which increased the metabolic need for vitamin A.

(5) Several had liver damage which prevented the proper storage of vitamin A or the conversion of carotene to vitamin A.

No attempt will be made to correlate vitamin A deficiency with all the diseases found in this group. The number of persons with each disease studied is too small for analysis. The study of a larger series, utilizing a portable photometer so that readings can be obtained from patients too sick to be moved, is at present under way and will be the subject of a later report. The results given here are really those of convalescent persons, and should not be taken as representative values of disease during its most severe manifestations. Undoubtedly, tests conducted on bed-ridden patients at the height of their illness will show an even greater degree of vitamin A deficiency than was present in members of group three.

Typical photometer readings obtained of persons from both groups two and three, who were considered to be either moderately or severely deficient, are tabulated in table 3. It can be readily seen that the photometer readings of this group are noticeably different from those of the control and mildly deficient group. Several persons in the moderately and severely deficient group had stigmata clinically suggesting vitamin A deficiency (i.e., dry skin, hyperkeratosis follicularis of the skin, dry conjunctivae or the subjective complaint of poor vision in dim illumination). Of the persons who saw the photometer light only through wedge opacity zero, one or two would usually complain of some manifestation of hemeralopia if carefully questioned. However, in most cases the degree of disability was not such as to cause them to seek medical advice specially for that complaint. In a group, at present under study, an attempt is being made to correlate photometer readings with these mild subjective and objective clinical evidences of vitamin A deficiency.

Frandsen [1] noted that persons with hemeralopia (as detected by tests for distinction power) often complained of palpitation, dry skin, dry mucous membranes, changes in sweat secretion, asthenopia, photophobia, *mouches volantes;* while the physical examination occasionally showed changes in the conjunctivae of a mild degree and dryness of the skin. Park [7] observed

that persons with very low photometer readings showed one or more of the following: general lack of vigor, easy fatigability, lack of luster of the cornea, nervous irritability, ptosis of eyelids and various visual difficulties including true night-blindness.

These studies serve to indicate that while vitamin A deficiency rarely causes serious trouble, it may interfere with the efficient functioning of the body and cause many vague and annoying disturbances which detract from the desirable vim and vigor of life.

TABLE III

Representative Photometer Readings Obtained on Persons Moderately and Severely Deficient in Vitamin A

Subject	Remarks	Initial Reading		Ten Minute Reading	
		Wedge	Diaphragm	Wedge	Diaphragm
Patient	Diabetes Mellitus	2	14	4	16
Patient	Hepatitis	0	20	1	14
Student	Disliked Many Foods	2	10	4	10
Patient	Active Malaria	3	10	5	10
Patient	Multiple Myeloma	2	12	4	12
Patient	Chronic Diarrhea	3	6	4	6
Patient	Bleeding Peptic Ulcer	3	4	4	6
WPA Worker	Chronic Sinusitis . . . Poor Diet	3	10	5	8
Patient	Early Cirrhosis	3	8	4	8
Patient	Portal Cirrhosis	2	8	4	14
Technician	Poor Diet	2	10	4	12
Patient	Cancer of Colon—Diarrhea	1	16	2	8
Patient	Ulcerative Colitis	2	10	3	6
Patient	Obstructive Jaundice	2	6	3	8
Patient	Generalized Carcinomatosis	1	10	2	6
Orderly	Poor Diet and Food Dislikes	4	14	5	10
Patient	Chronic Alcoholism	2	6	4	10
Patient	Lobar Pneumonia	2	6	5	12
Patient	Catarrhal Jaundice	3	14	4	12
Student	Poor Diet	3	8	4	14

VITAMIN A DEFICIENCY DUE TO DISEASE

Evidence of vitamin A deficiency may develop even though the daily intake of the vitamin is theoretically sufficient to supply the needs of the body. Vitamin A and the carotenoid substances must not only enter the body, but must be completely absorbed from the gastrointestinal tract as well as changed and stored in the liver before being ready for use by the body.

On a theoretical basis it can be predicted, and from the literature can be gathered much evidence to show, that vomiting, various types of gastro-intestinal and gastro-colic fistulae, changes in the gastrointestinal mucosa, lack of pancreatic secretion and chronic diarrheas can all hinder the proper absorption of vitamin A and carotene.[6, 7, 17, 20, 21] Evidence is also available

to show that there may be a differential absorption of pure vitamin A and carotene. Under certain conditions one may be absorbed where the other is not.[11] Where such pathological conditions exist it is necessary to increase the intake of vitamin A many times over normal to compensate for the inefficient absorption.

Three persons who were ambulatory and had diarrhea of at least six months' duration were tested with the photometer. The results are included among the results tabulated in table 3. Two were treated for four weeks with 10,000 units (U.S.P.) of carotene daily with no improvement in the photometer readings. Park [6] reports that where diarrhea existed in his patients no improvement was noted in the photometer readings if the usual oral dose of carotene was utilized. These results suggest that the dose of vitamin A in the presence of poor absorption must either be increased enormously or some vitamin A preparation given parenterally. Parenteral injections have been shown to be effective both experimentally [9] and in humans.[1, 79]

Since the liver serves to store vitamin A, release it according to the body needs and convert carotene to vitamin A, one would expect liver damage to cause vitamin A deficiency. It has long been known that liver disease could cause even clinically detectable vitamin A deficiency.[79, 80] Examination of livers post-mortem for the vitamin A content showed that livers with diffuse damage, caused by fibrosis, inflammation or tumor, had marked reduction in the amount of vitamin A stored.[13]

Photometer tests, both in the present series and in cases reported by Park [6] and others,[11] show that practically every patient with liver disease gave low readings. Of six persons with liver disease, who were able to be ambulatory, all gave low readings on the Birch-Hirschfeld photometer. The readings of four of these cases are included in table 3. The diagnoses included toxic hepatitis, catarrhal jaundice and portal cirrhosis. Two of these were treated with carotene with little or no change in the photometer reading. One woman with hepatitis took carotene, 20,000 units (U.S.P.) daily, for five weeks. In spite of this large dose, the photometer readings did not improve until the jaundice cleared, when within one week a change was noted. The patient was discharged before the study could be completed. Parenteral injection of vitamin A has been reported as successful in liver disease.[79] Since the liver serves to convert carotene to vitamin A, one would expect on theoretical grounds that vitamin A concentrates would be a better source of vitamin A than carotene. However, no data are available to show this.

Aside from absorption and storage, metabolic changes influence the amount of vitamin A needed by the body. Fever,[8] infection [17] and pregnancy [19] have all been shown to increase the need for vitamin A. Wendt [18] has shown in experimental animals that the presence in the blood stream of an increased amount of thyroxin diminished the vitamin A reserve. In

addition he was able to show that a high basal metabolic rate in humans increased the need for vitamin A. Not enough data have been collected yet to show what the photometer readings would be in persons with hyperthyroidism.

Park [6] has noted in his series of cases that persons with fever and infections of various types often had low photometer readings. Edmund [19] believes that pregnant women not only have a greater metabolic need for vitamin A but that gastrointestinal absorption of this vitamin is less efficient during pregnancy.

It is evident from the data already on hand that the subject of vitamin A deficiency in various diseases is extremely important and its significance only beginning to be realized.

Results of Therapy of Vitamin A Deficiency

Belief in the specificity of essential hemeralopia as a measure of vitamin A deficiency (whether detected clinically or by means of a photometer or other instrument) rests on the prompt disappearance of both the subjective and objective manifestations following vitamin A therapy.

Empirically it has been known since the time of Hippocrates [2] that certain types of hemeralopia would disappear when treated with liver. However, it remained for Bloch [80] and Blegvad [79] to correlate the lack of vitamin with essential hemeralopia, xerophthalmia, xerosis conjunctivae and keratomalacia.

Spence [30] noted that gross hemeralopia improved in three to five days and entirely disappeared in from seven to ten days when cod-liver oil and butter were given in large amounts. Aykroyd [31] and others [1, 81] have reported similar results.

Every investigator who has studied vitamin A deficiency by means of a photometer or determination of distinction power has noted a return to normal readings after a period of vitamin A ingestion. Frandsen [1] and Edmund [3] used cod-liver or halibut-liver oil concentrates and found that most readings became normal within three weeks. Jeans and Zentmire [4] used three teaspoonfuls of cod-liver oil daily and found that the recovery period varied from four days to six weeks, with an average of about 12 days. Later these same workers [72] noted that similar results could also be obtained with either cod-liver concentrates or carotene. Park [6] used carotene in oil (daily dose equivalent to 15 teaspoonfuls of cod-liver oil) and found that the photometer readings returned to normal in from six to 41 days.

The most striking proof that the vitamin A supply of the body controls the photometer reading and distinction power was presented by Edmund.[19] This investigator found that a single intra-muscular injection of a vitamin A preparation (40,000 I.U. per c.c.) brought about the disappearance of

hemeralopia and an improvement in the readings in the course of from seven to ten minutes.

In the present study, 14 of the persons in group two (healthy active adults) who showed low photometer readings were treated with vitamin concentrates with no change in their diet. Each person received daily a carotene capsule * containing 10,000 U.S.P. units of vitamin A activity. Each person was retested at the end of two, three and four weeks on the therapy. The results are tabulated in table 4. With one exception (where it took one month), the photometer reading returned to the normal range after either two or three weeks. Those with very low photometer readings noted a subjective improvement in the ability to see in the dark. One man believed his furuncles cleared for the first time in years. Several persons thought they had more "pep" than usual. Such subjective improvements are hard to evaluate and must be studied on a larger group with appropriate controls.

Of particular interest were three young women who ate at the same boarding house. All showed low photometer readings. The diet was adequate in calories but poor in vitamin A rich food. With no change in diet, one woman had a normal photometer reading after taking carotene for several weeks, while no change was noted in the others.

The results obtained here, plus data collected from the literature, suggest that 5,000 to 10,000 U.S.P. units of vitamin A, whether taken as cod-liver oil, vitamin A concentrates or carotene, will abolish all subjective and objective evidence of vitamin A deficiency even if the diet remains inadequate. However, if any disturbance is present which increases the metabolic need for vitamin A or hinders the absorption or storage, then far greater doses would be needed. It may also be necessary to resort to parenteral therapy.

Since many of the foods rich in vitamin A are relatively expensive, it is suggested that it would be cheaper in many instances to add some vitamin A preparation to the diet rather than attempt to increase the vitamin intake by adding foods rich in vitamin A. This applies in particular to institutions with limited budgets and persons of poor financial means.

A word of caution concerning the excessive use of carotene would be of value. If carotene is absorbed from the intestinal tract faster than the liver can convert and store it, the surplus may be stored in the body tissues and cause a yellow color (carotinemia) to appear. This condition may resemble jaundice, but is, however, neither a disease nor dangerous, and promptly disappears when the intake of carotene is curtailed. None of the subjects in this study developed carotinemia although carotene of dose 10,000 U.S.P. units was taken daily for periods as long as six weeks. Both Park [6] and Sandler [5] had instances of carotinemia in their series when the dose of carotene was pushed above this level.

* The carotene used in this study was generously supplied by the SMA Corporation of Cleveland, Ohio.

TABLE IV

Photometer Readings on Normal Persons Deficient in Vitamin A and Results after Vitamin A Therapy

Subject	Remarks	Photometer Reading before Vitamin A Therapy				Length of Time Vitamin A Therapy Was Given	Photometer Reading after Vitamin A Therapy			
		Initial Reading		Ten Minute Reading			Initial Reading		Ten Minute Reading	
		Wedge	Diaphragm	Wedge	Diaphragm		Wedge	Diaphragm	Wedge	Diaphragm
Student 27	Ate in restaurant. Poor diet for financial reasons.	3	8	4	14	2 weeks	4	10	6	8
Student 24	Ate at home—Poor choice of foods.	3	12	5	14	2 weeks	5	8	7	14
Student 27	Ate at home—Avoided foods rich in vitamin A.	2	14	4	12	2 weeks	5	10	7	10
Technician 21	Disliked all foods rich in vitamin A.	4	12	4	8	1 month	4	14	5	6
Nurse 26	Trying to lose weight. Avoided vitamin rich foods.	3	14	5	16	3 weeks	4	12	6	10
Student 24	Financial reasons—poor diet.	3	14	5	10	3 weeks	4	10	7	10
Technician 22	Poor diet for financial reasons.	3	16	5	14	2 weeks	4	12	6	10
WPA Worker 34	Poor diet—Lack of money.	3	20	4	14	3 weeks	3	2	6	18
Technician 20	Poor diet—Trying to lose weight.	3	12	4	14	2 weeks	4	10	6	12
Nurse 29	Trying to lose weight—Avoided vitamin rich foods.	3	14	5	16	2 weeks	4	12	7	14
Student 28	Ate in restaurant. Poor diet.	3	14	5	12	2 weeks	4	8	6	6
WPA Worker 37	Poor diet—Ate at home.	3	14	5	10	2 weeks	4	12	6	14
Technician 23	Poor diet—Financial reasons.	2	8	4	6	2 weeks	3	6	5	10
Student 26	Poor diet—Financial reasons.	3	16	4	8	2 weeks	4	10	6	14

Summary

1. The literature dealing with the physiology, biochemistry, pathology and clinical aspects of vitamin A deficiency is reviewed.

2. Night blindness (hemeralopia), in the absence of intra-ocular disease, is the earliest and most constant manifestation of vitamin A deficiency in adults.

3. In adults, night blindness may exist for years as the only manifestation of vitamin A deficiency.

4. Night blindness is associated with certain objective data which can be measured by means of special procedures. These serve as a quantitative estimate of the degrees of vitamin A deficiency and are particularly valuable in that they can detect deficiency long before it becomes clinically manifest.

5. The results of studying 274 adults by means of a Birch-Hirschfeld visual photometer and data collected from the literature show that mild to moderate degrees of vitamin A deficiency are common among many supposedly healthy adults.

6. Financial reasons, peculiarities in choice of foods, ignorance of a proper diet and a desire to reduce weight, were among the factors leading to deficiency.

7. Vitamin A deficiency may occur even if the amount ingested daily is theoretically adequate if any condition is present which (*a*) increases the metabolic need for vitamin A (fever, infection, elevated basal metabolic rate, rapid growth and pregnancy); (*b*) interferes with the proper absorption from the gastrointestinal tract; or (*c*) interferes with the conversion of carotene or storage of vitamin A in the liver.

8. Vitamin A deficiency is probably a constant feature of liver disease, and does not respond to the usual oral doses of vitamin A.

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CRYSTALLINE INSULIN *

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It is now 14 years since insulin was made available to the medical profession and the results of a vast experience with its effects are now at hand. About two years ago, a modified insulin, protamine insulin, was offered to the medical profession. One of the most interesting revelations that came with this new insulin was the limitations of the old insulin. When reports began coming in on the new insulin, we came to realize how many insulin-treated diabetics in the hands of highly experienced workers were not under good control at all. This admission should have its sobering influence and its good effects.

At this point, let it be said that the newer insulins are nothing other than the original insulin which has been more or less modified. It is as though the vehicle for insulin has been changed and the new vehicles are such that the insulin molecule which they contain is absorbed gradually, and therefore acts more slowly.

Crystalline Insulin

One of these newer insulins is crystalline insulin. Insulin was first crystallized by John Jacob Abel of Johns Hopkins University. It is the purest known form of insulin substance. Chemically, crystalline insulin is a complex protein obtained as the end-product of the bovine pancreas. It is a complex molecule which can be broken down into such amino-acids as lysine, cystine, histidine, arginine, leucine, tyrosine, phenyl-alanine, glutamic acid and proline. While up to the present time no one of these amino-acid fractions or any known combination of them has been found to produce the physiological effect of the whole crystalline insulin molecule, it is said to have been the hope of Abel that this complex molecule might be so altered, or combined in such a way as to leave it unaffected by the gastric and intestinal juices. When that is attained, oral administration of insulin may be realized and a great want will be met. Until that is achieved, insulin must be used by the injection method.

Insulin is an amphoteric substance. It has an iso-electric point and above and below this point there is a zone in which its solubility is variable. Beyond that zone the solubility of insulin is rapid and complete. The upper limits of this zone lie usually at a pH of 6.0 to 6.2. Dr. Melville Sayhun of Detroit has, however, prepared a new crystalline insulin whose solubility is complete only at a pH of 6.4 to 7.0. Its advantages may be stated in simple terms: An insulin of greater alkalinity is absorbed more slowly by the tissues and blood and this in turn slows down the glycolytic effects of the insulin molecule.

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This new crystalline insulin was released for clinical study about six months ago and we have been working with it since that time. Throughout our studies with this new preparation, we aimed at determining its clinical value on the basis of its effects in comparison with results already obtainable with standard insulin and protamine insulin.

Aims in Insulin Therapy

The physician treating a diabetic aims at the avoidance of hyperglycemia and hypoglycemia. He desires to accomplish this with a minimum number of injections, for reasons both of convenience and of economy to the patient. These aims will be attained when we have an insulin that will have a positive effect in lowering the blood sugar and one that will do it without getting beyond our control. The ideal insulin and the ideal dosage should stop short of producing insulin reaction or insulin shock; and its action should continue throughout the entire post-cibal absorptive period.

Method of Study

Our patients ordinarily receive a liberal carbohydrate and low fat diet, with a commensurate amount of insulin. The only change that we made in the routine of these patients was to substitute crystalline insulin for the standard or protamine insulin which they had been taking. On the appointed day, hourly blood sugars were taken from 8 a.m. to 9 p.m. and hourly specimens of urine were obtained. In the following charts, the solid line represents the level of blood sugar while on standard insulin; the broken line represents the level of blood sugar after the patient had been taking crystalline insulin for a period of three to 14 days. As nearly as possible, all conditions were made the same for the hospital and ambulatory patients.

Glycolytic Effect of Crystalline Insulin

To what extent crystalline insulin can accomplish this may be seen in the following examples:

Case 1. A diabetic patient was stabilized on diet alone and was nearly sugar normal about the eighth day in the hospital. He had not received insulin. An hourly blood sugar curve was made on the eighth day (chart 1). On the eleventh day, he was given 15 units of crystalline insulin at 8 a.m. and the hourly blood sugar curve repeated. The glycolytic value of the crystalline insulin is reflected in the relative position of the two curves on the chart. A further index of the relative values of these two curves is obtained by adding the milligrams blood sugar of every hour. Without insulin the total value is 3168 mg. On the day crystalline insulin was given, the total value of the curve was 2877 mg. It is very evident that the blood sugar was markedly lower after the crystalline insulin, the first and only dose the patient received. These are advantages in taking a patient having a moderate hyperglycemia and glycosuria. In such a case the work done by the insulin is measured with greater certainty.

A glance at this chart further shows that the immediate effect of crystalline insulin was to lower the blood sugar from 180 mg. to 77 mg. in three hours. It should also be noted that the blood sugar trend for the following nine hours was kept within bounds and that is important. Had we given this patient a larger dose, we may rightly assume that the blood sugar would have reached lower levels.

Case 2. Mr. T. had been using standard insulin for three years and was under satisfactory control. With standard insulin the sum total of his hourly blood sugar

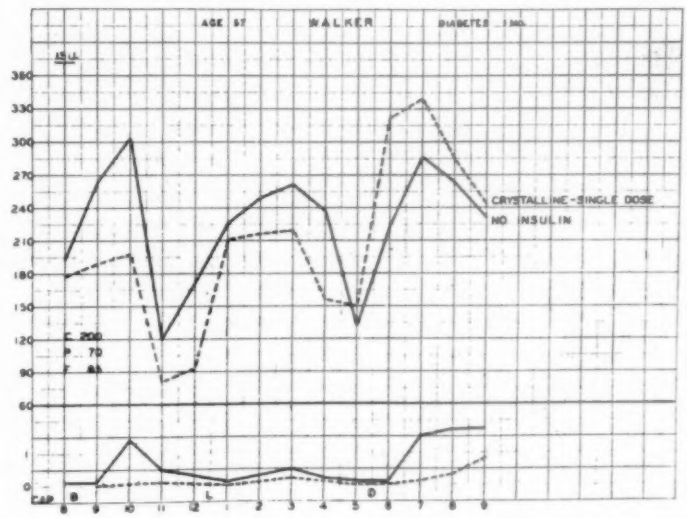

CHART 1. Hourly blood sugar curves. Solid line no insulin. Broken line crystalline insulin. Glycosuria depicted in lower curves.

curve was 3512 mg. After he had been on the same dose of crystalline insulin, which was substituted for his regular insulin, for seven days, an hourly curve for that day (chart 2) showed a total of 2660 mg. It will be noted that the fluctuations under crystalline insulin were smaller and the curve was comparatively level. It is interesting to note here that the insulins were given before the evening meal and while his blood sugar was quite high in the morning, it fell progressively during the day, regardless of his breakfast and luncheon having been taken without insulin. In part this may have been due to insulin, his own or that which was given him once daily.

CRYSTALLINE INSULIN SERIES

We repeated these experiments in a group of 21 diabetics, making daily curves while the patient was on standard insulin and again after a period of 3 to 14 days or longer on crystalline insulin. Out of these, we found that 12 patients showed a distinctly lower curve with crystalline insulin, while 9 showed a lower curve with standard insulin. In the 12 cases, crystalline insulin lowered the blood sugar to a greater extent and the entire curve remained at a more even level.

The following charts are typical cases which reacted well with crystalline insulin.

Total Effect of Crystalline Insulin

We constructed curves based on the average of blood sugar levels for the entire series of cases, as they were affected by both standard insulin and crystalline insulin (chart 8). In this study, we found that in the entire series of 21 cases, standard insulin kept the blood sugar at a lower level than crystalline insulin for a period of 36 units of time, while the same dosage of crystalline insulin kept the blood sugar at a lower level than the standard insulin did for a period of 125 units of time.

The deduction from these observations leads us to the belief that unit for unit, crystalline insulin accomplishes more than standard insulin.

Effect on Urine Sugar

Along with the hourly blood sugar, we also obtained hourly specimens of urine in these patients. Charts 1 and 3 are examples of the relative effect of crystalline and standard insulins on the total glucose metabolism. In a way, quantitative glycosuria reflects the glucose utilization even more completely than hourly blood sugars.

Duration of Effect: A Single Dose

In analyzing our curves, we find a marked difference in the length of time that a single dose of crystalline insulin affects the blood sugar curve in different patients. In the last analysis, this may represent the rate of insulin absorption. In our experience it was evident that in juvenile diabetics, absorption must be more rapid or factors yet unknown are at work.

Our observations reveal that whereas in the middle-aged or older diabetics crystalline insulin seemed to lower the blood sugar progressively for a period of 7.2 hours, in the young diabetics the downward curve was nearer 4.2 hours' duration. The cause of this is not always easy to estimate in a patient having three meals daily and more than one dose of insulin per day. Whether this variability in effect is due to rate of absorption or insulin sensitivity and insulin insensitiveness, is an unsettled question.

Crystalline Insulin Failures

There was one group of five cases in which the crystalline insulin curve was definitely not as good as the regular insulin curve. Of these patients, three were middle-aged diabetics and two were juvenile diabetics. In one of these young diabetics we repeated the experiment and found that standard insulin was better than either crystalline insulin or protamine insulin, as charts 9 and 10 will show.

Insulin Reaction—Shock

In going over the blood sugar curves and histories of the entire series, we found that insulin reactions and shock were four times as frequent in the

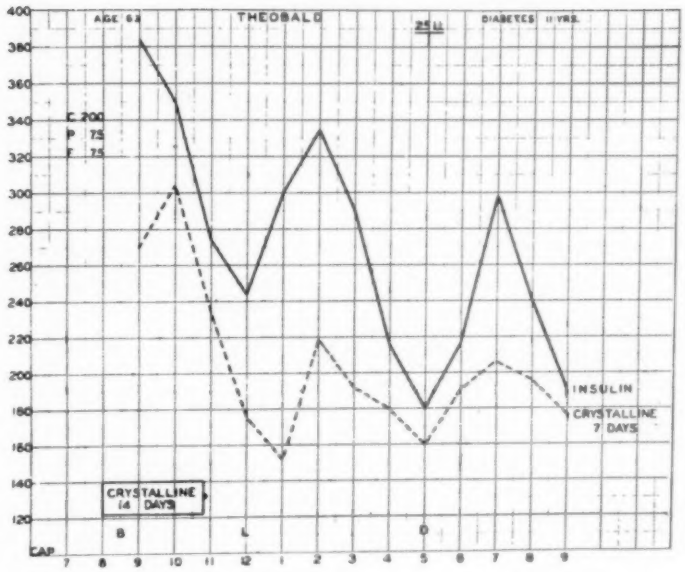

CHART 2. Hourly blood sugar curves. After 14 days on crystalline insulin, the morning blood sugar was 130 mg.

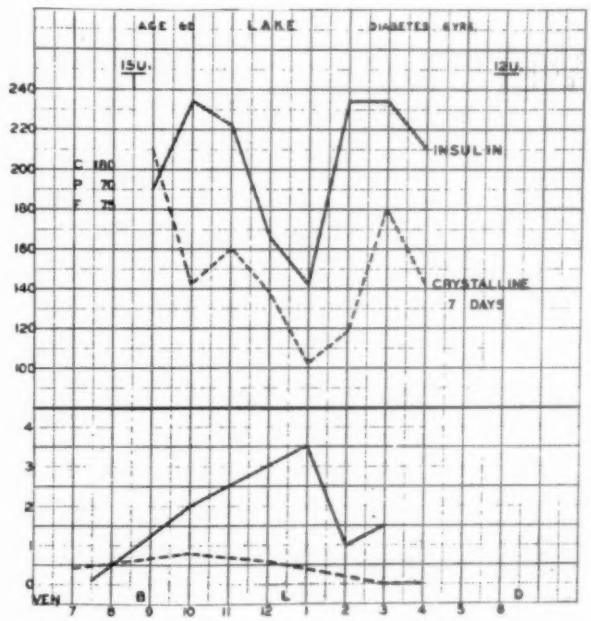

CHART 3. Blood sugar curve on standard and on crystalline insulin. Note curve of glycosuria, below.

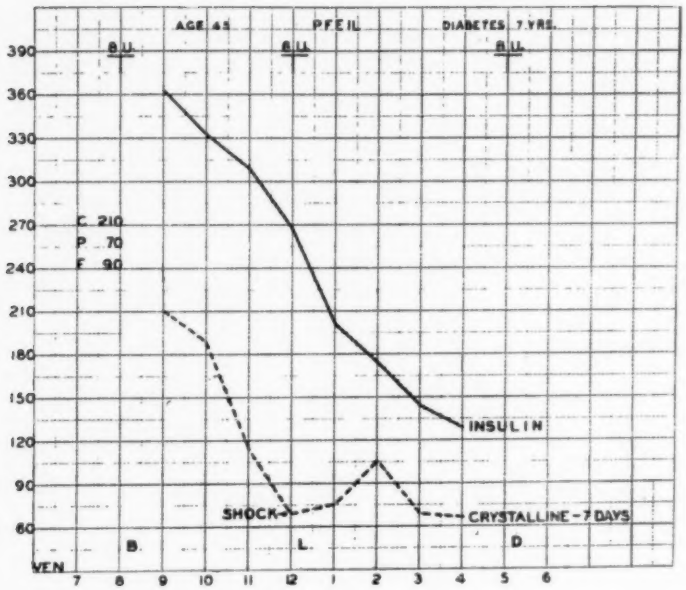

CHART 4. Blood sugar curves on standard and on crystalline insulin.

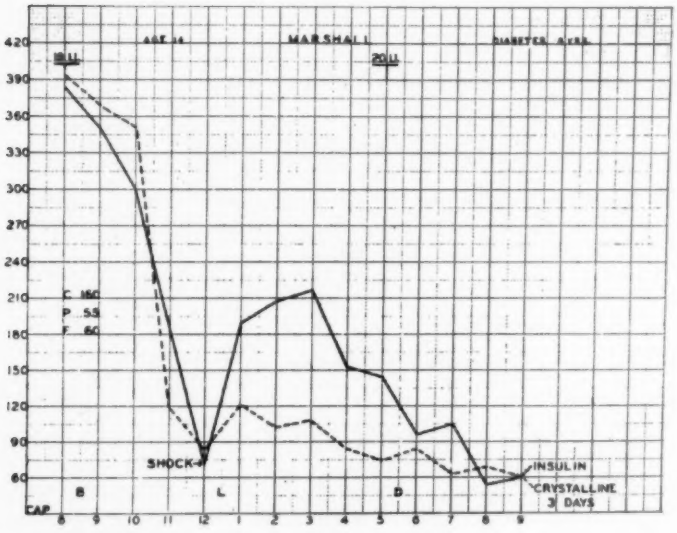

CHART 5. Blood sugar curves on standard and on crystalline insulin.

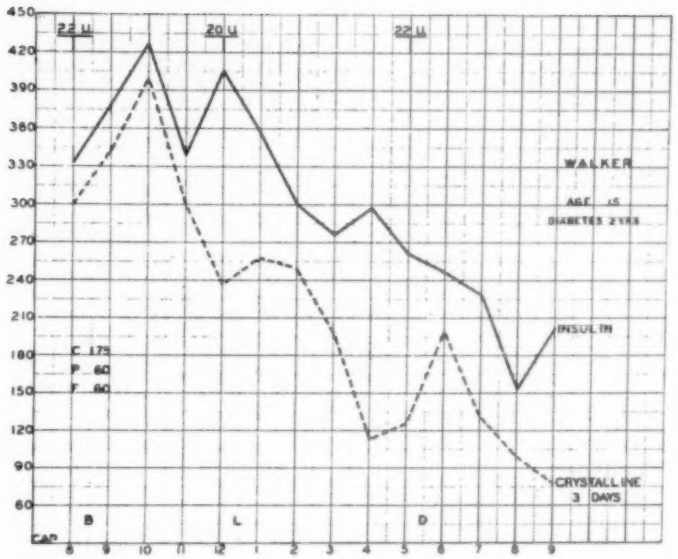

CHART 6. Blood sugar curves on standard and on crystalline insulin. Blood sugars by capillary method.

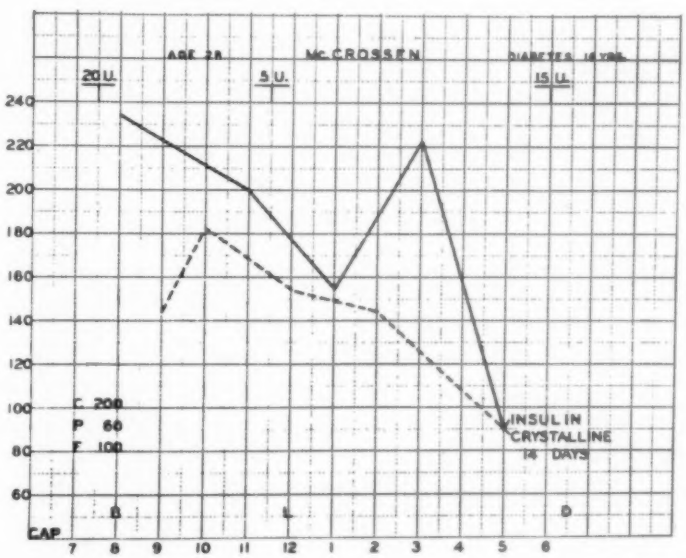

CHART 7. Blood sugar curves on standard and on crystalline insulin. Blood sugars by capillary method.

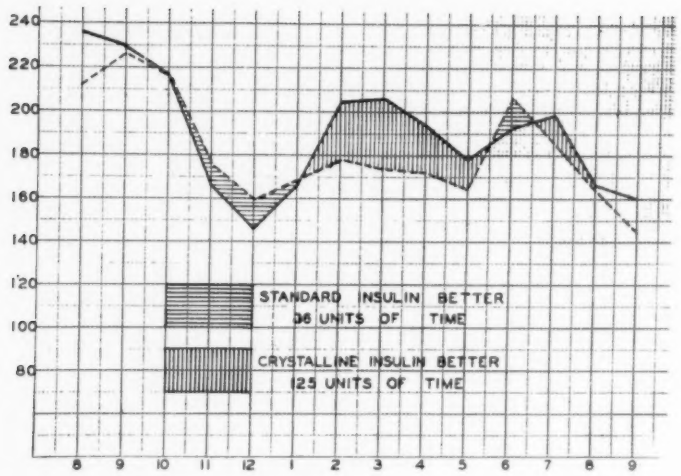

CHART 8. Glycolytic effects of crystalline and standard insulins in 21 cases.

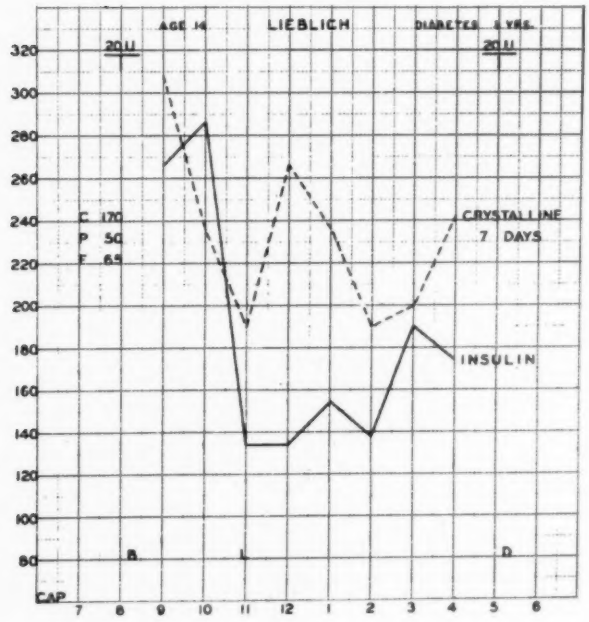

CHART 9.

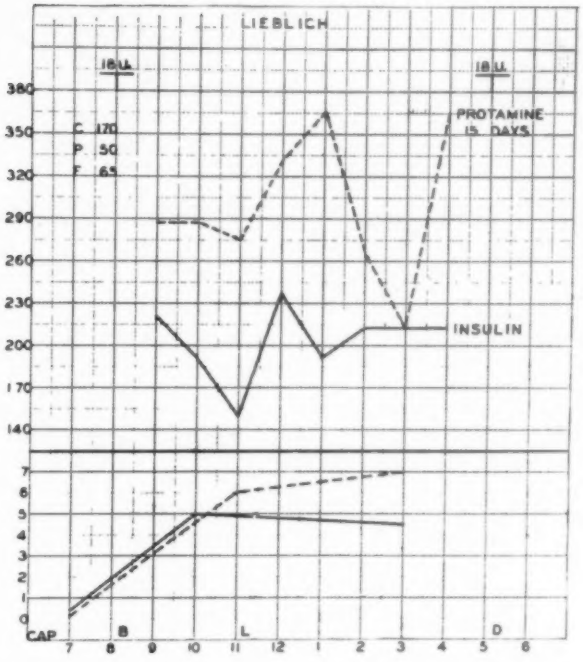

CHART 10. In this patient, standard insulin was distinctly more effective than crystalline or protamine insulin.

standard insulin periods as in the crystalline insulin periods. It was noteworthy that in crystalline insulin cases, when the blood sugar was in the 50 mg. zone at which time reactions usually begin to manifest themselves, these patients failed to show the usual symptoms.

SUMMARY AND CONCLUSIONS

Up to the present time, we have found no disadvantages whatever in the use of crystalline insulin, either in its administration or in its effects. Its sugar reducing value by every means that we could determine was actually greater than regular insulin in 12 out of 21 cases. It was less effective in 9 out of 21 cases. The absorption time of crystalline insulin is longer and its glycolytic effects are of greater duration. Insulin reactions or insulin shock occurred only one-fourth as often as when standard insulin was used. Because of its slower action and lessened tendency to produce shock, larger doses may be used to reduce the number of doses per day.

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LOBAR PNEUMONIA; AN ANALYSIS OF 1298 CASES *

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It is our purpose to analyze the cases of lobar pneumonia in patients admitted to the Buffalo City Hospital from January 1, 1927, to December 31, 1935. During that period 106,374 patients were admitted to the hospital, and of that number 1298, or 1.2 per cent were considered to have lobar pneumonia. Only those cases were included which represented unquestionably typical lobar pneumonia after critical evaluation of clinical records, radiographic findings and postmortem records. Roentgenograms were made in 40 per cent of the cases in this series, while necropsies were performed on 37 per cent of those patients dying of the disease. Of the 1298 patients, 787 recovered, while 511 died, a mortality of 38.5 per cent. It should be stated that in 32 per cent of the fatal cases, the patients died within 12 hours after admission, while nine were moribund upon arrival. If these patients are excluded, the corrected mortality is 37.8 per cent. Even this figure might be considered excessive by some authorities. However, Cecil [1] in a recent report on the death rate in pneumococcal pneumonia states that the death rate varies considerably with the class of the patient studied, being lowest in private practice, somewhat higher in hospitals treating the better class, and highest in hospitals treating purely indigent cases. Thus, the mortality at the Rockefeller Hospital is 19.5 per cent, and at the Bellevue Hospital 35.8 per cent.†

Despite the fact that pneumonia has dropped from second place in 1900 to sixth in 1934, it is still one of the leading causes of death. Metropolitan Life Insurance statistics [2] indicate that the 1934 death rate in pneumonia was 79.4 per 100,000 population. According to the New York State Department of Health,[3] pneumonia causes more loss of life in that state than any other single communicable disease and is exceeded as a cause of death only by heart disease and cancer. The annual loss of life from this cause in New York State alone is estimated at 12,000.

Mortality varies in some degree from year to year, month to month, and markedly so in respect to age incidence and the type of invading organisms.

This yearly variation with its concomitant mortality is clearly depicted in figure 1 and it is apparent that in the majority of years, the mortality rate paralleled the incidence. During the nine year period the lowest incidence was in 1932, while the highest was in 1929.

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From the Medical Service of the Buffalo City Hospital and the Department of Medicine, University of Buffalo.

† The Buffalo City Hospital in many respects resembles the Bellevue Hospital, being a municipal general hospital which receives and treats chiefly indigent patients suffering from all types of disease.

An investigation of the incidence of lobar pneumonia for the same period in Buffalo, N. Y.,[4] confirmed this observation. At the same time, reports gathered from various cities in the United States by the Metropolitan Life Insurance Company[2] revealed that this high pneumonia incidence prevailed

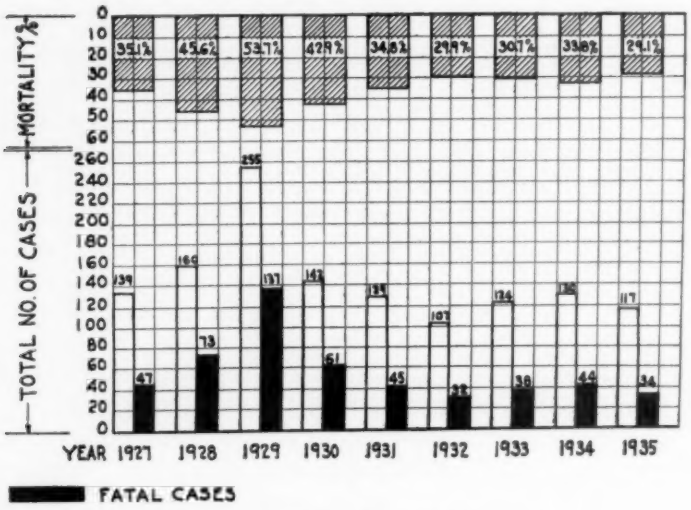

FIG. 1. Yearly incidence and mortality.

throughout the country. It was evident from a study of the yearly snowfall and mean temperatures in Buffalo,[5] that 1929 was not particularly remarkable from this standpoint. Analysis of typing in the present series

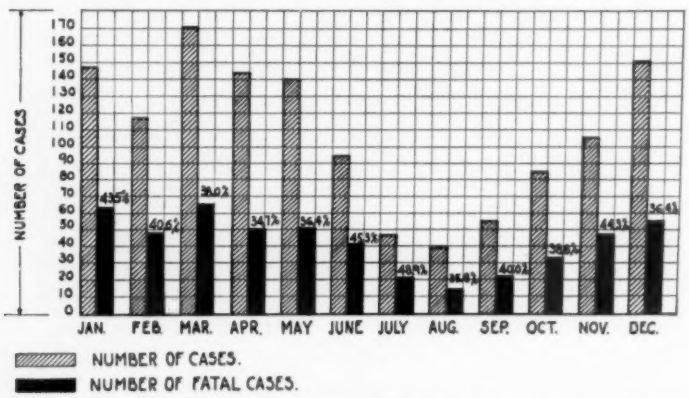

FIG. 2. Monthly incidence of pneumonia and mortality. For period 1927–1935 inclusive.

failed to show any predominant type during that year. No explanation is offered except that the country at large was the victim of a mild epidemic.

It is generally true that lobar pneumonia occurs chiefly during the cold winter months, December through March, but figure 2 indicates quite defi-

nitely that April and May on the average produce approximately as many cases as all of the winter months except March. It is also important to note that though the incidence was lowest in the summer months, the mortality rate in summer was actually higher than in the corresponding winter months. An effort was made to determine if meteorological conditions in any way influenced the incidence of pneumonia. Although no absolute relationship could be traced, the highest incidence peaks occurred during months in which precipitation and snowfall were greatest, and the average mean temperature low. This is shown in figure 3.

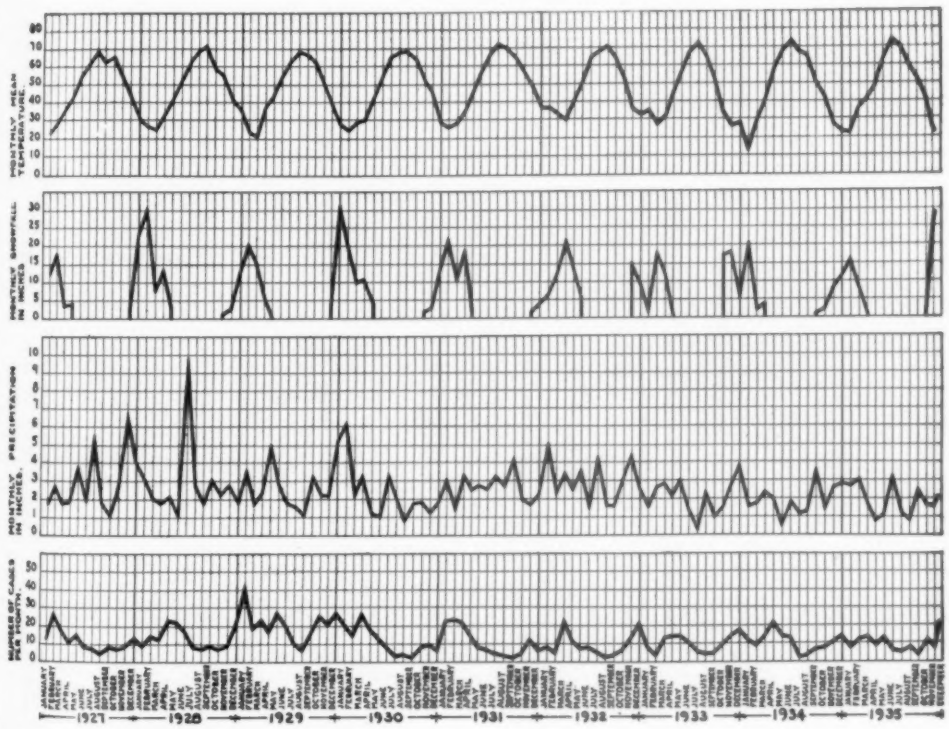

FIG. 3. Incidence of lobar pneumonia in relation to precipitation, snowfall and mean monthly temperature.

SEX

It is generally believed that lobar pneumonia, like most serious diseases, occurs more often in men than in women. In this series of 1298 patients, 969 patients were men and 329 patients were women, a ratio of about three to one (figure 4). The mortality among women was 31.9 per cent, while in the men, the mortality was 41.9 per cent or exactly 10 per cent higher. This greater incidence and the increased death rate in men most likely was based on such factors as occupation with its subsequent exposure, mode of living, and alcoholic indulgence.

Color

Negroes in Buffalo comprise 2.4 per cent of the total population. In this series 23.2 per cent of the patients were colored, 2.2 per cent were American Indians, and the remainder, 74.5 per cent, were white people. Despite the fact that colored races are generally much more susceptible to respiratory ailments, including tuberculosis, the mortality was higher in the white patients than that in either the negro or Indian patients. This is graphically shown in figure 4.

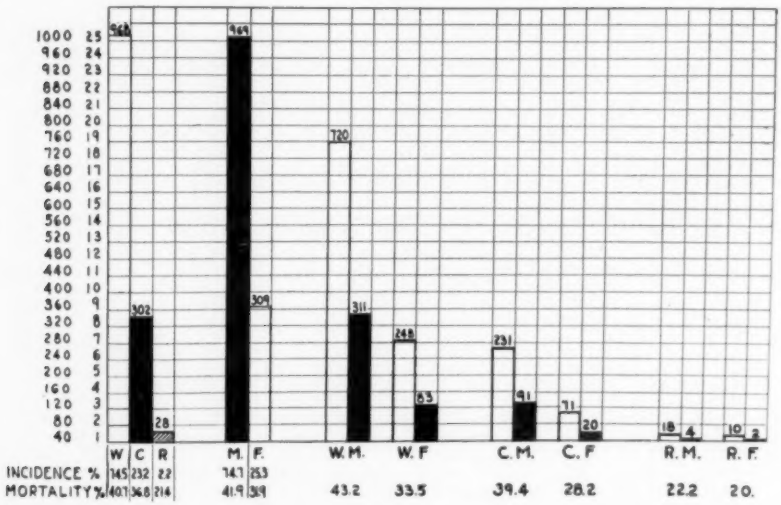

Fig. 4. Relationship of color and sex to incidence and mortality.

W—White.
C—Colored.
R—Indian.
M—Male.
F—Female.

Age

Figure 5 demonstrates the effect of age upon the incidence and the death rate. It is clear that lobar pneumonia is a very serious disease in infants under one year. As children become older the mortality rate gradually declines until the age period of five to ten is reached when it strikes its lowest ebb (9.5 per cent). From that age until senility, the death rate progressively increases in a direct proportion to the age.

The highest incidence periods seem to lie between 20 and 50. Fifty-three per cent of the patients who developed the disease were within this age period. The single decade showing the highest incidence occurred between the ages of 30 and 40.

Symptoms

The onset of lobar pneumonia is usually described as abrupt. Musser[6] states that antecedent respiratory infection had occurred in slightly over 40

per cent of the Rockefeller Hospital patients. Sudden onset in 58.1 per cent of our patients was followed by a mortality of 31.7 per cent, while in 41.9 per cent who started gradually the mortality was 29 per cent. If the assumption is true that those patients who experienced a gradual onset were in reality the victims of a previous respiratory infection, it is evident that the so-called common cold was actually the precursor of lobar pneumonia in 42 per cent of the cases. Whether or not the type of onset bore any prognostic relation to the mortality is not demonstrated.

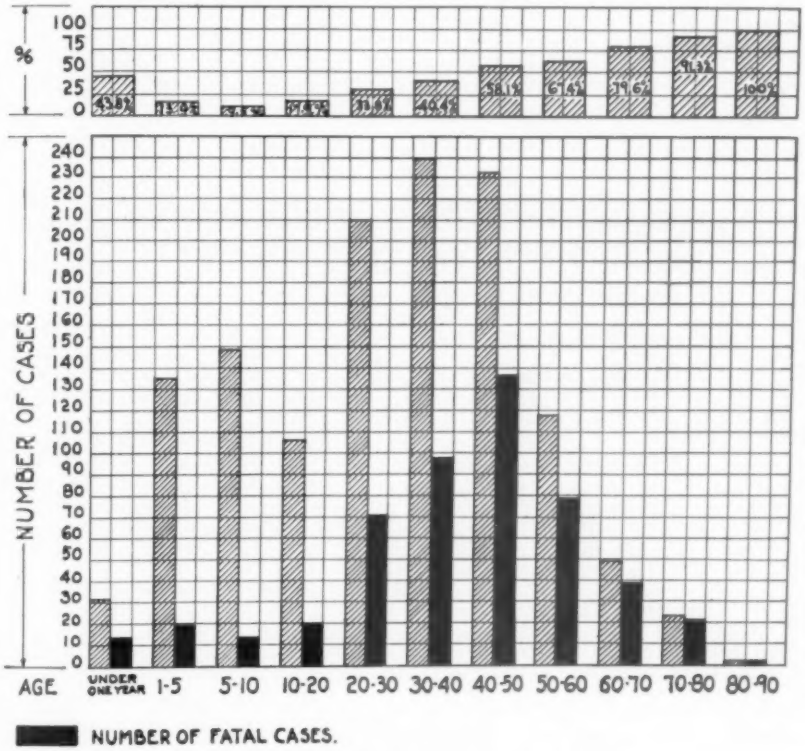

FIG. 5. Age incidence and mortality.

The common cardinal symptoms were considered, such as cough, pain in the chest, chills, dyspnea, and hemoptysis, along with the complicating symptoms, cyanosis, ileus and hiccough. The relative incidence of the various symptoms is shown graphically in figure 6, together with the mortality of the aforementioned complicating symptoms. Although most textbooks list the chill as the most common characteristic symptom, figure 6 clearly indicates that the dry hacking cough was the most constant symptom in this series. Obviously this symptom, because of its frequent occurrence in practically all respiratory diseases, is not pathognomonic of lobar pneumonia, but combined with the other symptoms shown in the table, produces valuable

clinical leads. Pleural pain, which is generally regarded by pathologists as the result of stretching of adhesions, was the next most common symptom, occurring in 61.1 per cent of the patients, and even though second in frequency was still nearly twice as common as chill. The latter symptom, typical chill, occurred in only 33.2 per cent of the patients although more complained of mild chilly sensations. It is interesting to note that Reginald Fitz,[7] in Peter Bent Brigham Hospital, found only a slightly higher percentage (37 per cent). While the respiratory rate was increased in practically every instance, some patients complained of marked difficulty in breathing. This dyspnea was present in 22.2 per cent. Hemoptysis, the fifth most common symptom in frequency, occurred in only 21.5 per cent of the patients. It should be mentioned that only manifest bloody sputum was considered hemoptysis; blood-streaked or blood-flecked sputum was excluded.

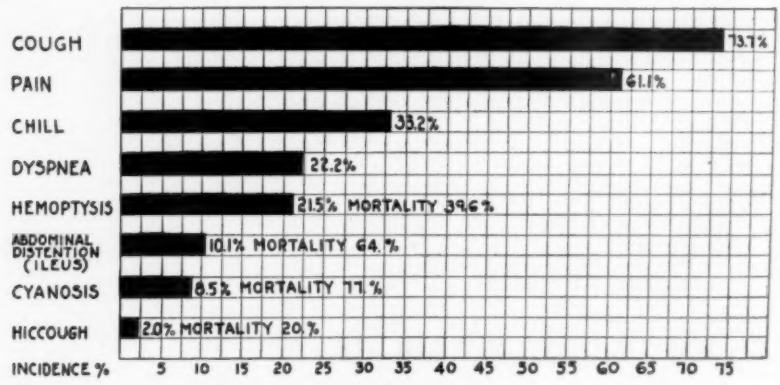

FIG. 6. Incidence of symptoms in lobar pneumonia.

Cyanosis, ileus and hiccough, though usually regarded as signs, are included in this discussion as complicating symptoms because the latter two frequently occur late in the course of the disease. Our criterion of cyanosis was definite blueness of the lips, fingernails and face, and did not include transient or mild duskiness. It is apparent from figure 6 that although of rather infrequent occurrence, it was an ominous sign.

Marked abdominal distention as a result of ileus is also a serious complicating symptom. It was found in only 10.1 per cent of the patients but carried with it a mortality of 64 per cent. This symptom is probably an expression of profound toxemia upon the sympathetic nerve endings controlling the small intestine.

Hiccough, a rather rare symptom, occurred in only 2 per cent of the cases with a 20 per cent mortality.

From time immemorial lobar pneumonia has been considered the one disease that terminates abruptly by crisis. Cecil,[8] on the contrary, feels that the majority of cases decline gradually by lysis. Only 54.5 per cent of our

patients who recovered had a sudden fall in temperature; in the remainder the temperature fell gradually by lysis.

At this point it seems advisable to recapitulate with an evaluation of symptoms according to the commonly accepted pathogenesis of the disease. Blake and Cecil [9] have demonstrated that the primary pathologic process in the development of pneumonia is a penetration of the walls of the larger bronchi by the pneumococci. This process in addition to the tracheobronchial infection gives origin to the dry hacking cough which was not only the earliest but the most frequently observed symptom. Following the penetration of the bronchi, the organisms pass along the lymphatics of the fibrous septa in a rapid centrifugal direction until the periphery is attained. In the wake of this process the alveoli are reached and ultimately perforated by the pneumococci. This sequence makes it apparent that the exudative process which results in consolidation really starts at the hilus and proceeds peripherally. At the same time the foregoing statement in a measure explains why pleural pain was the second most common symptom. This conception of the pathogenesis of pneumonia may serve as an explanation for the fact that a chill occasionally is observed after the occurrence of cough and pleural pain, and in this series occurred in only one-third of the patients. Both dyspnea and cyanosis are expressions of anoxemia which many authorities feel is due to fluid on the inside of alveoli preventing the diffusion of gases. It seems likely that dyspnea is the result of a moderate anoxemia; while cyanosis, with a mortality of 77 per cent, is a manifestation of grave oxygen lack.

At the same time, it seems quite apparent that the symptoms should be the earliest manifestation of the pneumonic process and precede the development of outspoken signs of clinical consolidation by a matter of hours varying from 12 to 48. We noted this frequently.

Lobar Involvement

Comparisons were made in this study in an effort to determine the relative incidence and mortality of individual lobar involvement, multi-lobar involvement, and the various frequency of upper and lower lobe solidification. This is clearly portrayed by figure 7. Right-sided involvement, including single and multiple lobe consolidation, occurred in 754 patients (58.1 per cent) with 300 deaths (39.8 per cent). Left-sided lesions, considered in a similar fashion, occurred in 462 patients (35.6 per cent), with 162 deaths (35.1 per cent). It is apparent that lobar pneumonia was much more frequent in the right lung, but the mortality considered as a whole was only slightly higher in this location. A comparison of the frequency of involvement of the upper lobes as opposed to the lower lobes reveals that the right and left upper lobes were individually affected in 18.5 per cent of the patients (mortality 29.6 per cent) while the lower lobes were individually attacked in 48.1 per cent of the patients (mortality 33.8 per cent). This

indicates that individually the right lower and the left lower lobes were attacked 2½ times as often as the upper lobes. The ratio is practically the same as that found by Warr and Alperin [11] who reported the lower lobes involved twice as often as the uppers.

Similar comparative studies of lobar involvement with relative frequency and mortality rates are described by many writers. Cecil [8] found the right side involved 666 times and the left 598 times. In his series, the right lower and the left lower lobes were involved in about equal frequency of all single lobar lesions. Right and left lower lobe consolidation was by far

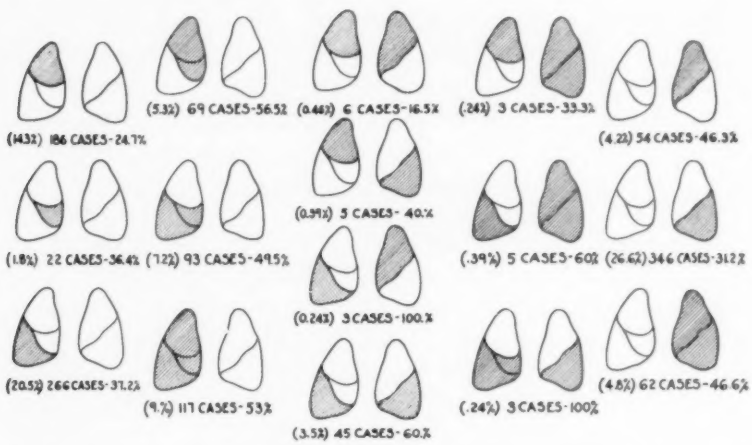

FIG. 7. Lobar involvement in 1298 cases of lobar pneumonia with percentage of mortality.

Note: Figures in parentheses indicate percentage of incidence of various lobar involvement.

Consolidation is indicated by cross hatching.

Rt. Upper and lower—1 case—0 per cent.
Rt. Lung and left upper—2 cases—50 per cent.
Rt. Lung and left lower—2 cases—50 per cent.
Rt. Upper and middle and left upper—2 cases—100 per cent.
Rt. Upper and middle and left lower—1 case—100 per cent.
Rt. Upper and lower and left upper—1 case—100 per cent.
Rt. Upper and lower and left lower—1 case—100 per cent.
Rt. Middle and left lower—2 cases—50 per cent.
Rt. Upper and middle and entire left—1 case—100 per cent.

the commonest bilobar combination. His conclusions were that the seriousness of the disease varied directly with the number of lobes involved. This is in agreement with McCrae [10] who, quoting statistics from 100 autopsies performed at the Montreal General Hospital, reported right-sided lesions in 51 and left-sided lesions in 32. Both lungs were involved in 17. In 29 cases the entire lung was involved, and in 34 merely the lower lobe was affected. The upper lobes alone were affected 13 times. When double, the lower lobes were usually consolidated together, but in three instances the lower lobe in one lung and the upper lobe in the other were solidified. Only in three were both upper lobes affected.

Just why the lower lobes are more often affected than the upper lobes is speculative. If it is assumed that approximately 40 per cent of the patients developing lobar pneumonia have previous respiratory infection, and that lobar pneumonia, as Coryllos and Birnbaum [12] have shown, is essentially a pneumococcal atelectasis due to a bronchial obstruction from a catarrhal plug, the anatomy of the bronchial tree with the right and left bronchus practically continuous with the main bronchus, makes it appear quite logical that the plug should eventually locate in these lower bronchial passages.

Single Lobar Involvement

In discussing monolobar consolidation, it is apparent from figure 7 that the left lower stood out as the most frequently involved lobe, occurring in slightly more than one-quarter of the cases in the entire series (346 cases). Despite the marked frequency of involvement in this particular lobe the mortality was only 31.2 per cent, considerably less than the adjoining upper lobe or the opposite lower lobe. The next most frequent single lobe affected was the right lower which occurred in 20.5 per cent with a mortality of 37.2 per cent. The right upper lobe was third in frequency with an incidence of 14.3 per cent. The left upper lobe was involved in only 4.2 per cent, but was associated with a high mortality (46.3 per cent). Peculiarly enough, although right-sided lesions are almost twice as frequent as left-sided lesions, and although the middle lobe in many cases is almost an integral part of the right upper, this lobe was involved in only 1.8 per cent with a mortality of 36.4 per cent.

Multilobar and Bilateral Lobar Involvement

While Harlow Brooks [13] concluded from his series of 200 autopsied cases that the extent of lung involvement was but of minor value as a prognostic factor in death in lobar pneumonia, many observers, including the authors, have felt that it is one of the important contributory influences producing a fatal outcome.

The following table tends to corroborate this latter viewpoint, and indicates quite distinctly that mortality in multiple lobar involvement is directly proportionate to the number of lobes involved.

It is interesting to note that pneumonia in more than one lobe occurred

Table I

Extent of Lobe Involvement in 1298 Cases

Number of Lobes Involved	Total Cases	Fatal Cases	Per cent Mortality
One	874	286	32.7
Two	286	148	51.7
Three	133	74	55.6
Four	5	3	60.0

in about one-third of the entire series, which is slightly higher than the percentage found by Warr and Alperin [11] who found multiple lobar involvement in only one-quarter of their series. These authors also stated the mortality was higher when the disease was bilateral than when two or more lobes of one lung were involved.

J. A. Ryle [14] of Guys' Hospital, writing on the prognosis of lobar pneumonia, is of the same opinion and lists excessive bilateral involvement as the most serious of unfavorable factors in determining prognosis.

Table 2 substantiates the contention that bilateral involvement materially increases the mortality rate and adds to the seriousness of the prognosis.

TABLE II

Bilateral Bilobar Involvement

Lobes Involved	Total Cases	Fatal Cases	Per cent Mortality
Both lowers	45	27	60.0
Both uppers	6	1	16.5
Left lower and right upper	5	2	40.0
Left upper and right lower	3	3	100.0
Right middle and left lower	2	1	50.0
Total	61	34	Av. 55.7

ALCOHOL

Evidence of alcoholic poisoning, manifested chiefly by delirium tremens, was present in 73 patients (figure 8). All were men and 58, or nearly 80

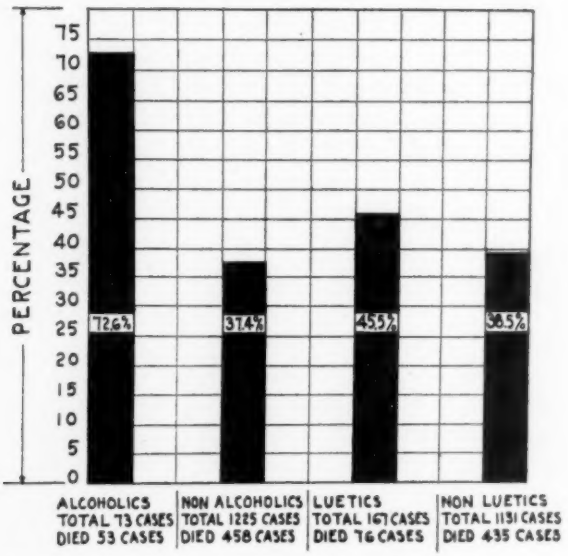

FIG. 8. Per cent of mortality in alcoholics and luetics as compared to non-alcoholics and non-luetics.

per cent, were white. Fifty-three patients died with a resultant mortality of 72.6 per cent. This mortality is almost double that of the non-alcoholic patients. One might expect a higher percentage of alcoholic patients in a large series such as this, but it should be remembered Harlow Brooks [13] found histories of alcoholism in only five of his 200 postmortem cases. Undoubtedly there are many more patients who were alcoholics of some degree but were not the severe chronic drinkers who might be expected to develop delirium tremens.

Some observers have felt that chronic alcoholism predisposes to certain lobe involvement. In the present series 22 per cent of the total number of alcoholics developed a right lower lobe pneumonia, while in 18 per cent it was in the left lower lobe. This is interesting as left lower lobe pneumonia occurred in 27 per cent of the total number of patients, while right lower lobe consolidation occurred in 21 per cent of the total number. Although the percentage difference is relatively small, it seems that alcoholics developed processes in the right lower lobe more often than in any other single lobe. No explanation is offered for this coincidental finding.

Relationship to Syphilis

Of our 1298 patients, 167 or 12.8 per cent had a positive Wassermann reaction, and of this number, 76 died and 91 recovered, a mortality of 45.5 per cent. This figure is 7 per cent higher than the mortality for the whole series or for the non-luetic group (see figure 8). Seventy-two (43.1 per cent) patients were white, 93 (55.7 per cent) were colored, and two (1.2 per cent) were Indians. The large number of colored patients does not explain this increased mortality as it was shown in figure 4 that the mortality actually is higher in the white race.

It was also thought that possibly fatalities occurred here because of increased age and the presence of late cardiovascular lues. Investigation revealed that these fatal cases were quite evenly distributed throughout the age groups. Only four of the fatal cases showed gross luetic meso-aortitis on postmortem examination. The relationship to typing was inconclusive.

Again a survey of various lobar involvements was undertaken in the 167 patients with lobar pneumonia and syphilis to establish whether any particular lobar predilection existed. The lower lobes were attacked in 41 per cent of the cases, the uppers in only 16.2 per cent, and the middle lobe in only 1.8 per cent. The right lower and left lower lobes were involved almost equally.

The problem of delayed resolution or unresolved pneumonia was also considered in its relationship to syphilis. This complication was relatively uncommon in this series as it occurred in only 27 patients (1.8 per cent). Of these, only four (14.8 per cent) had a positive Wassermann test. These observations are essentially the same as those made by Weinstein and Goodman [15] (Johns Hopkins Hospital) who considered that delay in resolution

TABLE III

Complications

	Total Cases	Incidence	Recovered	Died	Mortality %	Type I			Mortality %	Type II			Mortality %	Type III			Mortality %	Type IV			Mortality %	Untyped			Mortality %	Strep.			Mortality %
						R.	D.	T.		R.	D.	T.		R.	D.	T.		R.	D.	T.		R.	D.	T.		R.	D.	T.	
Empyema	120	9.3%	46	74	61.7	19	8	27	29.6	5	2	7	28.6	1	1	2	50	5	1	6	16.7	16	61	77	73	0	1	1	100
Pleural effusion	62	4.8%	40	22	35.5	4	2	6	33.3	2	2	4	50	1	1	2	50	5	0	5	0	28	17	45	37.8				
Otitis media	48	3.6%	44	4	8.3	4	0	4	0	2	0	2	0	2	1	3	33.3	0	0	0	0	36	3	39	7.7				
Chronic fibrous pleurisy	37	2.8%	35	2	5.4	6	0	6	0	5	1	6	16.7	1	0	1	0	5	0	5	0	18	1	19	5.3				
Pericarditis	28	2.1%	4	24	85.7	1	5	6	83.3	1	0	1	0	0	0	0	0	0	3	3	100	2	16	18	88.9				
Unresolved pneumonia	24	1.8%	21	3	12.5	3	0	3	0	4	0	4	0	0	0	0	0	1	0	1	0	13	3	16	18.8				
Lung abscess	16	1.2%	5	11	68.8	0	1	1	100	1	0	1	0	0	0	0	0	0	1	1	100	4	9	13	69.2				
Meningitis	13	1.0%	0	13	100	0	1	1	100	0	2	2	100	0	1	1	100	0	3	3	100	0	6	6	100				
Bronchiectasis	14	1.08%	2	12	85.7	0	0	0	0	0	1	1	100	0	0	0	0	0	0	0	0	2	11	13	84.6				
Tuberculosis	10	.77%	4	6	60	1	1	2	50	1	0	1	0	0	0	0	0	1	0	1	0	1	5	6	83.3				
Jaundice	10	.77%	3	7	70	2	0	2	0	0	0	0	0	0	1	1	100	0	1	1	100	1	5	6	83.3				
Peritonitis	3	.23%	0	3	100	0	1	1	100	0	0	0	0	0	0	0	0	0	1	1	100	0	1	1	100				
Atelectasis	3	.23%	2	1	33.3	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	100				
Arthritis	2	.15%	1	1	50	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Cellulitis	2	.15%	2	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0				
Pleuro-pericarditis	1	.077%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Abscess rt. arm	1	.077%	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
Pyoarthrosis	1	.077%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Pyelonephritis	1	.077%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100	0	0	0	0				
Cellulitis of scrotum, and penis	1	.077%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Left parotitis	1	.077%	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Totals	395		211	184		44	19	63		22	8	30		5	5	10		19	11	30		128	141	269					

of the pneumonic process occurred almost as frequently in the non-syphilitics as in the syphilitics.

Leukocyte Count

The total leukocyte count has long been regarded as an index to prognosis in lobar pneumonia. It is usually conceded that a good leukocytic response indicates that the patient's fighting forces are mobilized to combat the invader. Total leukocyte studies were made on slightly more than 70 per cent of the patients in the present analysis. Figure 9 demonstrates quite clearly that the optimum total leukocyte count to ensure a good prognosis lies between 30,000 and 40,000. It is also evident that as the total leukocyte

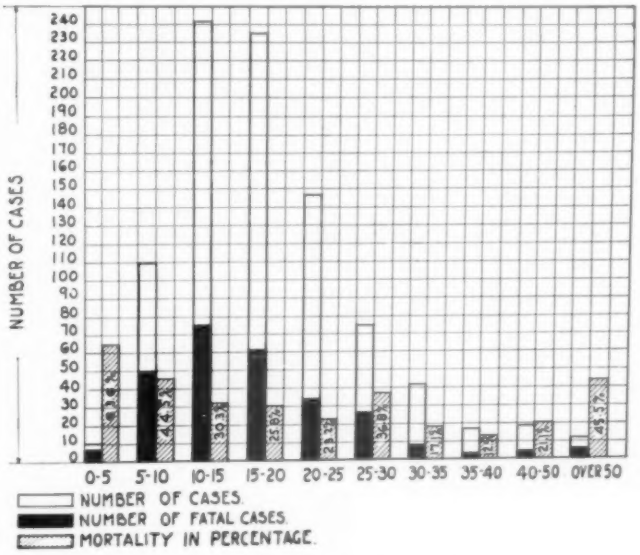

Fig. 9. Total leukocyte count in thousands.

count decreases from 10,000 downward, the mortality increases in a direct proportion. This is to be expected because diminished resisting forces permit the infection to overwhelm the patient. At the same time, as the total count increases over 50,000, the mortality rate progressively increases. This might be explained by the probability that even though the bone marrow was actively responding to the infection, the toxemia was so profound that death ensued as a result of its degenerating effect upon the heart, higher brain centers and periphero-vasomotor nerve endings.

During the past few years considerable attention has been directed to the differential count as advocated by Schilling. It is generally accepted that the so-called " shift to the left " with an increasing output of young forms indicates a doubtful prognosis. In this survey, total polymorphonuclear leukocyte counts were analyzed, without deriving evidence therefrom;

Schilling counts were performed only during the years 1934 and 1935 so that conclusions are unwarranted at this time.

Typing

The type of pneumococcus was ascertained in about one-quarter, 313, of these patients. This rather small number was due to the fact that the procedure was relatively difficult and expensive during the years preceding 1934, but with the advent of the Neufeld method in 1935, this difficulty has obviously been overcome. However, it is interesting to note (figure 10) that

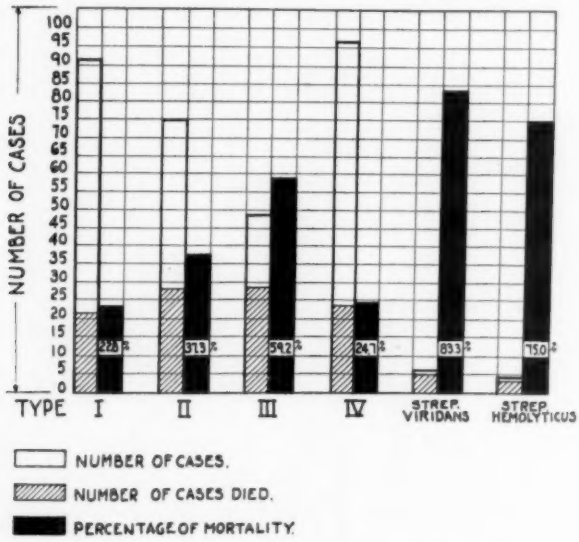

FIG. 10. Typing and percentage of mortality.

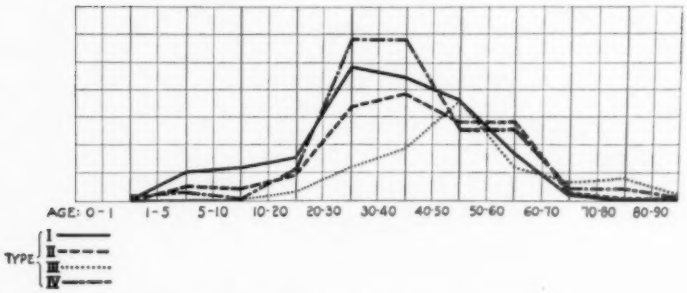

FIG. 11. Relationship of age incidence to type.

the incidence is greatest of types I and IV and lowest of type III. At the same time, the mortality rate of type III was approximately twice that of any of the other types, or equivalent to the mortality of any two other types. These observations are not new and have been previously stated by Cecil [8]

and other authors. It also can be seen from figure 2 that type I and to some extent type II were most common in the patients under 40, while type III occurred more frequently than any other type in patients over 40. This partially accounts for its high mortality rate and also for its relatively low incidence.

It also will be seen from table 3 that type I was the most frequent producer of complications, particularly empyema. On the contrary, type III seldom or rarely produced complications. This paucity was probably related to the fact that nearly 60 per cent of these patients died in the acute phase of the disease before complications usually occur.

Complications

Empyema, in our experience, was the most common complication. It is to be remembered that empyema is always a complication and never a sequel. One hundred and twenty patients (9.3 per cent) developed pus in the pleural space. This high incidence requires a few words of explanation. In 69 patients (57.5 per cent) the diagnosis of empyema was tentatively made by clinical examination and confirmed by paracentesis. Of these, 46 recovered and 23 died (mortality rate 33.3 per cent). In 13 of the other 51 cases diagnosed at autopsy, there was a rather massive empyema, while in 38 there was present only a purulent exudate on the pleura. The latter finding was designated fibrino-purulent pleurisy, which may be classified as empyema because this type of pleuritis is in reality a localized or loculated empyema. Therefore, in 82 patients there were rather large collections of pus in the pleural space, while 38 others merely developed a purulent appearance of the pleura itself. Many writers feel that if all fatal cases of pneumonia were autopsied, the recognized percentage of empyema would be considerably higher, and it appears that this series supports that viewpoint. However, if the cases showing only fibrinopurulent pleurisy were excluded, the incidence of empyema is 6.3 per cent, which is approximately the percentage found by Cecil [8] and his co-workers. McCrae [10] basing his statistics on the Johns Hopkin's series, found only 3.6 per cent, while Musser [6] estimates the incidence as being between 3 and 5 per cent. Warr and Alperin,[11] in their large series of 2,039 cases, found an empyema incidence of only 2.6 per cent. It is quite likely that 7 or 8 per cent would be a more accurate figure if all fatal cases of lobar pneumonia were investigated post mortem. Then, too, a great deal depends on whether one is to include rather minute collections of pus in the pleural space as empyema. The mortality rate in empyema in this series was 62 per cent.

Pleural effusion was the second most frequent complication, occurring in 62 patients (4.8 per cent). This figure was considerably higher than that found by Warr and Alperin,[11] who recorded only eight pleural effusions in 2039 lobar pneumonias. Joules [16] reported only five effusions in his series of 496 cases. Both of these figures seem low, if it is borne in mind

that in our series only 22 of the 62 effusions were discovered by postmortem examinations. The remaining 40 diagnoses of pleural effusion were made by clinical examination, roentgenographic studies and confirmed by paracentesis. In all probability most lobar pneumonia is accompanied by slight pleural effusions which are not diagnosed due to lack of sufficient quantity or hesitancy and fear of aspiration.

Next in frequency was otitis media. This complication occurred in 48 patients (3.6 per cent). It was by far the major complication in childhood. Forty-two of the 48 cases occurred under the age of 10. This complication can be considered relatively mild in severity as the mortality was only 8 per cent, or less than the general mortality for the age group from 1 to 10 years.

Chronic fibrous pleurisy also was a frequent complication but it is such a natural pathological sequela to the pneumonic process that further discussion is unnecessary.

Pericarditis was next in frequency occurring in 28 patients (2.1 per cent). The mortality was 85.7 per cent, making this complication one of the gravest. The majority of cases occurred in left-sided lesions which was to be expected inasmuch as pleuritis, pleuro-pericarditis and visceral pericarditis is the usual pathologic sequence.

Unresolved pneumonia or delayed resolution occurred in only 1.8 per cent of the patients. The relationship to syphilis has been discussed. Tuberculosis has been thought to be responsible for many unresolved processes, but in this survey positive evidence of superimposed tuberculosis was rare, as will be brought out later.

Lung abscess was also a relatively rare sequel, developing in only 16 patients (1.2 per cent). This incidence was slightly higher than the Bellevue series of 2122 cases, where only 9 cases were observed. The mortality was exceedingly high, ending fatally in 11 (69 per cent).

Meningitis, the most severe of all complications or sequelae, occurred in 13 patients (1 per cent) terminating fatally in all cases. This outcome must be expected as meningeal involvement is practically always the result of an overwhelming pneumococcal septicemia.

Other complications, such as bronchiectasis, tuberculosis, jaundice and peritonitis, occurred rather infrequently. Bronchiectasis was present in 14 cases (1.8 per cent), 12 of which were discovered post mortem. Apparently it is extremely rare in patients recovering from the disease. Ten patients subsequently developed tuberculosis. It is, therefore, suggested that series showing a higher incidence of tuberculosis possibly include acute pneumonic forms of tuberculosis. Jaundice also occurred in 10 cases with a mortality of 70 per cent. The mechanism of jaundice in lobar pneumonia is rather obscure. Some observers feel that it is chiefly hemolytic, while others attribute it to parenchymatous hepatic degeneration. It is probably a combination of the two processes and in either event is expressive of profound toxemia and warrants a poor prognosis.

Fatal peritonitis occurred in 3 cases and obviously rates in the same category as meningitis as a complication which foretells a fatal termination.

The other complications tabulated were so rarely observed that discussion is of little consequence.

Treatment

The problem of evaluating treatment was attacked with some trepidation. Lobar pneumonia, like many other diseases, has run the gamut of therapy, but the consensus of modern authorities resolves the treatment into oxygen and specific serum when indicated. In this series an attempt has been made to draw some conclusions from the various drugs and therapeutic measures used in the past nine years (figure 12).

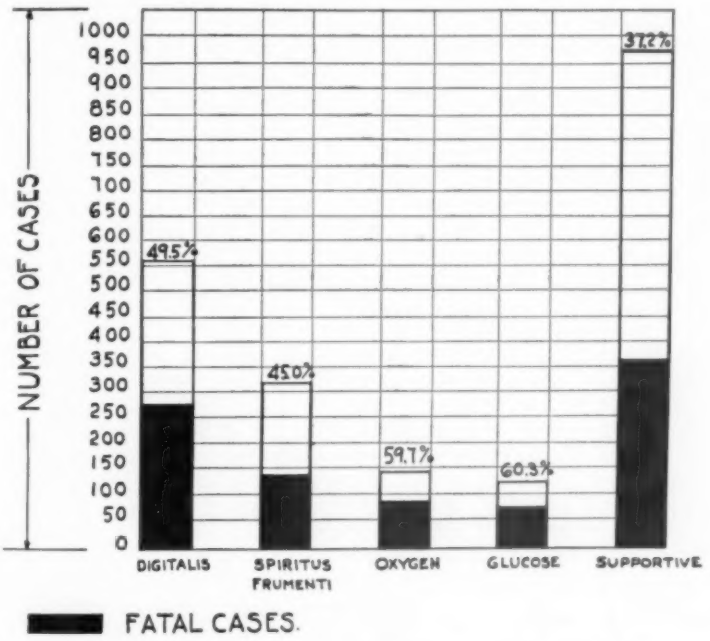

Fig. 12. Therapy of lobar pneumonia with mortality.

The first drug considered was digitalis. This was used in 557 patients with a mortality of approximately 50 per cent. The majority of those who received digitalis entered the hospital during the years 1927 to 1930. All were digitalized routinely. During the past few years, Cohn and Lewis,[17] working at the Rockefeller Institute, have shown that the mortality is actually higher in the digitalis-treated groups. Inasmuch as the mortality in our patients treated with digitalis was nearly 50 per cent, this conclusion seems to be well-founded. Since 1930, digitalis has been used in pneumonia

cases only when such indications as grave cardiac irregularities, auricular fibrillation or congestive failure developed.

The second type of therapy investigated was the use of alcohol in the form of whiskey. This drug was largely used by our medical forefathers and is still used routinely by many physicians today. In 320 patients treated with routine doses of whiskey the mortality was 45 per cent, or 7 per cent higher than the general mortality. This drug, like digitalis, has also been discontinued during the past few years and is now reserved specifically for the chronic alcoholic who, in the face of pneumonia, may develop delirium tremens if it is omitted.

Oxygen, the third most commonly employed therapeutic measure, was administered to 149 patients with a mortality of approximately 60 per cent. To the casual observer, this high mortality might be interpreted as minimizing the value of this form of therapy. Some explanation is obviously necessary. Most of the patients who received oxygen were cases showing marked cyanosis, dyspnea or grave circulatory failure. In other words, the majority of these cases probably would have ended fatally whether or not oxygen were used. It should also be stated that the majority of these patients received oxygen by means of the mask, which is now known to be the least effective method of administration. The cases treated in this fashion obviously occurred in the days prior to the use of nasal catheter or the development of oxygen tents and oxygen chambers. Only a few of the patients were given oxygen early in the course of their disease. There is no doubt in our minds that early oxygen therapy, given by the proper methods, is a valuable therapeutic agent.

Glucose (20 per cent dextrose) was given intravenously to 121 patients, and was followed by a 60 per cent mortality. The same applies to glucose as applied to oxygen, namely, that this drug was also used in cases of evident circulatory failure where an unfavorable outcome was anticipated. Even with this high mortality, we believe that the use of this drug intravenously often turns the tide in a favorable direction.

The last form of therapy investigated has been listed under the general term of "supportive treatment." By this term is meant the use of any drug, which can be employed to support the patient in a general way. The judicious use of morphine, codeine, caffeine sodium benzoate, salicylates and quinine may be considered under this heading. The latter drug was used in about 90 per cent of the patients treated by so-called "supportive measures." It has a long reputable record in pneumonia therapy. During the past decade, a closely related drug, optochin, has been highly regarded as a pneumococcicidal agent. Inasmuch as no one has proved any deleterious effect, and, as there may be some beneficial result from quinine administration, it has been retained as a routine therapeutic measure. It should also be mentioned that the combating of toxemia through establishing improved water balance by means of forced fluids orally, and saline administered parenterally is also a valuable and important factor included under the term

"supportive measures." Likewise good nursing care must be included under this blanket term. The patients treated merely by "supportive" treatment had the lowest mortality, 37.2 per cent.

Pneumothorax was used in seven selected cases with only one death. This number is too small to draw any conclusions therefrom.

Specific type I serum was also used in such a small number of cases that any clinical deductions are unwarranted.

Summary and Conclusions

An analysis has been made of the records of 1298 patients having lobar pneumonia observed at the Buffalo City Hospital from 1927 to 1935, inclusive.

The mortality rate for the entire series was 38.5 per cent.

The incidence of lobar pneumonia and the mortality rate varied considerably from year to year.

The incidence of lobar pneumonia varied materially from month to month but regardless of whether it occurred in the winter or summer, the mortality was approximately the same.

The mortality rate was highest at the extremes of life and lowest between the ages of five and ten. From ten years to old age, the mortality was directly proportional to the age.

Lobar pneumonia was three times as common in men as in women and the mortality rate was approximately 10 per cent higher.

The mortality rate among northern negroes was less than in the white race.

The mortality rate in chronic alcoholics was approximately twice that of non-alcoholic patients.

The presence of syphilis materially increased the mortality rate, although no relationship was demonstrated between syphilis and delayed resolution.

Chill was not as common a symptom as has previously been believed.

Lobar pneumonia, involving one or more lobes of the right lung, was one and one-half times as frequent as left-sided involvement. Multi-lobar involvement and bilateral involvement add considerably to the mortality rate and the gravity of the prognosis.

Leukopenia, and leukocytoses above 50,000 were serious prognostic findings.

Type IV pneumonia was the most commonly observed type, while type III was accompanied by the greatest mortality. The greatest number of complications was observed in type I, while the least was seen in type III. Type III was the most commonly observed type in patients over 40, type I being the preponderant type in adolescence and early life.

Empyema, pleural effusion, and otitis media were the most frequent complications in the whole series, while pericarditis, meningitis and peritonitis were the most fatal.

The effect of routine therapeutic measures upon the mortality rate was inconclusive.

The authors wish to express their appreciation to Dr. Carroll J. Roberts for his valuable suggestions and criticisms, and to Drs. V. Boeck, D. Levy, and A. Cirrincione for their assistance in the compilation of the statistics.

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FURTHER OBSERVATIONS OF THE HISTIDINE TREATMENT OF PEPTIC ULCER*

By Ellis W. Willhelmy, M.D., *Kansas City, Missouri*

In 1923, Mann and Williamson [1] reported that they were able to produce in dogs subacute and chronic peptic ulcers, quite like those found in man, by diverting to another part of the intestine those secretions of the duodenum which normally neutralize the gastric juice as it leaves the stomach.

Aron and Weiss [2] of Strasbourg repeated and confirmed these studies. They came to the conclusion that these ulcers formed as a result of an amino acid deficiency. On this theory, they gave intramuscular injections of certain amino acids to dogs that had been subjected to the Mann-Williamson technic, and found that daily injections of 5 c.c. of a solution of 4 per cent histidine and 2 per cent tryptophan would prevent the development of ulcers in the dog. This experimental work was followed by clinical trial in ulcer patients with marked success, according to their report.

In the due course of time following the publication of Aron and Weiss, other encouraging communications on the use of histidine in the treatment of peptic ulcer began to appear in the foreign literature and eventually, largely through the extensive advertising claims of one of our pharmaceutical companies, the physicians of this country were informed of this work and the results reported by European investigators.

The treatment of peptic ulcer constitutes such a major therapeutic problem that any plausible aid that holds the possibility of a cure or the elimination of the usually accepted, protracted routine of bed rest, milk, alkali powders and diet over a period of months, seems to us to be worthy of consideration; so, with this thought in mind, we began to treat a series of peptic ulcer patients with a series of 24 daily intramuscular injections of 5 c.c. of 4 per cent histidine monohydrochloride.†

Since January 1935, we have treated 42 roentgen-ray proved cases of peptic ulcer. Of these 42 cases, we have been able to carefully follow and recheck closely the clinical and radiographic progress of 28 cases, all of which have been observed for at least one year following the treatment. Due to the natural vagaries of ulcer symptoms, we called attention in an earlier preliminary report [3] to the necessity of conservative conclusions on immediate results. However, in view of the fact that most remissions in ulcer patients will not last for as long as a year, we feel that although our series is small, we can at this time draw fairly accurate deductions as to the value of the treatment, both from the standpoint of immediate and final results.

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† Larostidin—Hoffman-LaRoche, Inc.

In order that the conclusions from this study might be judged entirely on the effect of this treatment alone, these patients were requested to carry on their usual activities of life, were given no medicine whatsoever, and advised to eat a general diet. This latter suggestion was somewhat difficult to carry out inasmuch as most of these patients had already taken one or more medical cures and were aware of the efficacy of frequent feedings and alkalies. The patients who obtained relief with the first few injections were quick to branch out on their diet, but the more resistant cases were reluctant to take on foods that they felt had formerly caused trouble.

These cases were in no way selected but routinely placed on the treatment when they presented themselves to the clinic, regardless of the nature of their ulcer. By this method of choice, it is obvious that some cases of perforating and stenosing ulcers which could not normally be expected to respond to medical therapy were included in the series; so, we have shown in the following charts not only the results obtained in the entire series, but also the results obtained in 21 selected cases. The latter group was composed of such cases as showed uncomplicated peptic ulcer and no other physical ailment.

The group is composed of 17 males and 11 females, whose ages varied from 20 to 72 years, the average being 45.2 years (table 1).

TABLE I

Age and Sex

Age	20–29	30–40	41–50	51–60	61–70	71–80
Male	2	5	4	2	3	1
Female	2	3	3	3	—	—

Average age ..... 45.2 yrs.
Total males 17
Total cases 28
Total females 11

A history of typical ulcer symptoms, with intermittency, food and alkali relief, and epigastric distress two to four hours after meals, was presented in about 90 per cent of the cases (table 2). Four of the patients had had previous hemorrhages. Two cases gave a history of perforation and three cases presented an entirely atypical symptomatology, the diagnosis being

TABLE II

Symptomatology

Epigastric pain or distress	25 cases
Intermittency	26 cases
History of food and alkali relief	24 cases
Hemorrhage	4 cases
Perforation	2 cases
Atypical symptomatology	3 cases
No food or alkali relief	4 cases

Avg. duration of symptoms 8.8 years.

established entirely by roentgen-ray findings. The average duration of symptoms was 8.8 years.

Of the 28 cases in the series, 23 were duodenal and five were gastric ulcers (table 3). The roentgen-ray findings were rechecked every three months for one year and at the end of this time two cases of the duodenal

TABLE III
Radiographic Results

Duodenal	
Cured	2 cases
Improved	5 cases
Unimproved	16 cases
Gastric	
Cured	0 cases
Improved	0 cases
Unimproved	5 cases

ulcer group were considered cured. This deduction was based on the disappearance of all deformity of the cap, as well as a clinical course in which there had been no recurrence of symptoms. Decreasing size of the crater, improvement in the appearance of the bulb, and decreasing activity of the stomach were the criteria on which five cases in the duodenal group were considered improved radiographically. Sixteen of the duodenal cases were unimproved from the roentgenologic viewpoint. None of the five cases of gastric ulcer showed any improvement radiographically. Analyzing these figures, we find that approximately 75 per cent of the cases showed no improvement radiographically, while 8.6 per cent were considered cured and 21.7 per cent improved.

The clinical results of the entire series show six cases or 21.4 per cent received complete and total relief (table 4), a figure considerably higher than the percentage considered cured radiographically, but a percentage quite in keeping with the radiographic findings if we consider the number of cases

TABLE IV
Clinical Results in Entire Series

Duration of Symptoms	No. of Cases	Complete Relief	Partial or no Relief	Complete Relief with Relapse
1–3 yrs.	7	3	2	2
4–5 yrs.	3	0	2	1
6–10 yrs.	10	3	3	4
11–14 yrs.	3	0	2	1
15–20 yrs.	3	0	1	2
21 plus	2	0	1	1
Total cases	28			

cured and improved radiographically. This discrepancy is possibly due to the fact that some cases cured clinically may not have been considered cured radiographically because of a remaining scar in the duodenal cap. Eleven cases, or 39.3 per cent, received only partial or no relief; and 11 cases, or 39.3 per cent, received complete relief but relapsed within the first year following treatment. Adding the percentages of the relapsing group to those that received only partial or no relief, we find approximately 80 per cent of the patients received no real permanent benefit from the treatment. However, if we group the relapsing cases that received complete relief with those that received permanent relief, we find that 60 per cent of the patients obtained symptomatic relief, a percentage somewhat lower than our experience with the Sippy management of peptic ulcer.

In the group of 21 selected cases, we find 28.6 per cent of the cases received permanent relief, 23.8 per cent were complete failures, and 47.6 per cent received complete, immediate relief with relapse within the first year (table 5). This group of cases probably more nearly represents the true curve of success and failure, as the stenosing and perforating cases were not included in the final deductions.

TABLE V

Clinical Results in Uncomplicated Cases

Duration of Symptoms	No. of Cases	Complete Relief	Partial or no Relief	Complete Relief with Relapse
1–3 yrs.	7	3	2	2
4–5 yrs.	2	0	1	1
6–10 yrs.	7	3	1	3
11–14 yrs.	2	0	1	1
15–20 yrs.	2	0	0	2
21 plus	1	0	0	1
Total cases	21			

Ten of the patients from the selected group were given a second course of treatment four to six months after finishing the first course, regardless of whether or not they had relapsed within that period. It is interesting to note that of this group, those patients who had previously relapsed have all developed symptoms again following the second course of treatment.

One uncomplicated case has received four courses and has relapsed within 30 to 60 days following each course, although he received complete relief from symptoms during each period of treatment. Sandweiss [4] has reported that several of his cases became symptom-free with a daily intramuscular injection of water. We are of the opinion that possibly the above case would be an excellent subject on whom to determine the psychological effect of injection treatment.

Two uncomplicated cases have received three courses of treatment, and all have relapsed from three to seven months after the treatment. The case that relapsed seven months after the treatment shows the longest period of freedom from symptoms that we have found in the relapsing group.

Two of our cases have been operated upon four to six months respectively after the completion of the injections, and in both instances active ulcers were present. One other case died of intra-abdominal complications four months after completing the treatment, and an active duodenal ulcer was found at the necropsy.

In our earlier report, we were of the opinion that the cases in which symptoms had not been present longer than five years were the ones most likely to be benefited; but in the final analysis, we find three cases cured who had had symptoms from six to 10 years, and three cases whose symptoms were less than five years in duration. So it is apparent that the duration of the ulcer has made no difference in the final results except from the standpoint that none of the remaining cases with symptoms for more than 10 years received any improvement.

It has been our experience that most of the patients who received complete relief became symptom-free with the first few treatments; and those cases who received no early benefit did not improve with increasing the number of treatments, as we gave several patients 30 daily injections. One case received 38 daily treatments with no improvement whatever, but became symptom-free on a carefully managed Sippy routine. We have experienced no reactions in any of the 42 cases we have treated and are of the opinion that the treatment is perfectly harmless.

In conclusion, we would like to call attention again to the fact that this treatment will undoubtedly produce remissions in a fairly high percentage of uncomplicated ulcer patients, 76.2 per cent in the selected series, but the permanent relief is no greater than that in various other methods of ulcer treatment and management. We have purposely not used the histidine treatment in conjunction with dietary and alkali routine because we felt that if the treatment were worth while, one of the greatest advantages it offered was the possibility of eliminating the monotonous routine of our usually accepted measures. We also felt that if peptic ulcers were due to histidine deficiency, as proposed on theoretical grounds by the originators, dietary measures would not be necessary. We were able to produce a remission with histidine in only one case of the four in whom dietary and alkali regime had previously failed to give relief. After two years' experience in the treatment of 42 patients with histidine, we are of the opinion that the results obtained do not justify the routine use of this procedure in the management of peptic ulcer patients.

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STUDY OF HYPERTENSION IN VETERANS*

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IN the period from October 1, 1935 to April 1, 1936, the Veterans' Administration Facility in Washington, D. C., discharged 1369 patients who had been under observation and treatment in the wards. Of this number, 82 had hypertension, which is approximately 6 per cent of the total number discharged. Riseman and Weiss [1] quote reports from two European hospitals in which the incidence of hypertension among the male patients examined was 9.6 per cent and 9.7 per cent respectively, and among the female patients 7.9 per cent and 25.9 per cent of the total number of women. In these reports, however, a blood pressure above 140 mm. Hg systolic was considered abnormal, while in this series, the figures of 150 mm. Hg systolic and 90 mm. Hg diastolic have been used as the dividing line. The diagnosis of hypertension depends to some extent upon the examiner, the conditions under which the examination is made, and the reactions of the patients; thus, a single estimation of pressure may be too high, particularly if the patient is under emotional stress. Alvarez [2] reported hypertension in 53.6 per cent of drafted men, which suggests that the emotional tension of an examination under such conditions increased the blood pressure of a considerable number of healthy men.

The present group under study is composed of veterans of the military services of the United States who were patients in this hospital. Many of them were observation cases and had not previously known of their hypertension.

Only 4.7 per cent of the whole discharged group were females of whom six comprised 7.3 per cent of the hypertensive group.

Among the men, the colored patients represented 8.2 per cent of all discharged and 20.7 per cent of the hypertensive cases. This disproportion is sufficiently great to indicate a greater incidence of hypertension in negro men than in white patients from the service groups.

A characteristic of the population in Veterans' facilities is the limited age period into which the majority of the patients fall. While the range for approximately 1600 patients was from 23 years to 92 years, the average was 45 years with 58.5 per cent between 40 years and 49 years. The average age of all the hypertensives was 49.8 years or approximately five years older than the whole group, with 51 per cent between 40 and 49 years. The colored patients with hypertension averaged 45.5 years of age, while the females with hypertension averaged 52.3 years. The latter group is too small to influence the figures greatly or to be more than suggestive of the trend, but it is significant that the Negroes not only have a relatively higher

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incidence of hypertension but the average age at which they appear for treatment is less than that of the white patients (table 1).

TABLE I
Incidence of Hypertension

	Controls		Hypertensives	
Age	Number	Per cent	Number	Per cent
20–29	6	0.3	1	1.2
30–39	374	23.3	11	13.4
40–49	937	58.5	42	51.2
50–59	188	11.7	10	12.2
60–69	73	4.6	12	14.6
Over 70	24	1.5	6	7.3

War Service and Post War Occupation

Sixty-four patients in this group were in the Service during the World War, one was a veteran of the Civil War, 11 were Spanish-American War veterans, and the remainder were in peace-time service. Among the World War veterans, 32 were overseas, and some engaged in varying amounts of combat service. The records show that six of these received gunshot wounds which in themselves were not severe enough to cause permanent disability, 10 claimed to have been gassed, in most cases with mustard gas, and a total of 26 gave histories of illness or injuries at home or abroad during their service, that may have affected their health subsequently. It is inferred that these men were physically fit upon entering the Service and were more or less disabled following their war-time experiences, although there is no common factor unless it be emotional strain that might account for the development of hypertension.

In many instances, high blood pressure and its complications have not been the reason for seeking medical care. Five patients have been unable to do any work or very little work since discharge from Service. One was discharged because of an injury to his back with subsequent hysterical manifestations, one had a gunshot wound followed by empyema, one had measles with severe complications, one was apparently well on discharge but developed symptoms and signs of serious cardiac disease within two months after discharge, one has been only partially active following pneumonia, and one has worked very little since the Service but did not have a medical record during his enlistment. Another veteran worked intermittently until 1928 but had some degree of heart failure since 1918.

With the exception of the traumatic disabilities, the illnesses most frequently noted were influenza, pneumonia, and rheumatism of various types. The Spanish War veterans usually gave a history of having had malaria, and one man who developed malaria in 1919 stated that he had not been well since. One veteran, who was in the Navy, made over 225 deep-sea dives up to 170 feet and was always sick after coming to the surface as he was

not decompressed. He has an excessively high pressure which has disabled him since the age of 32. It is impossible to say how important these illnesses and traumatisms were in causing hypertension, but in 19 of the 26 cases with wartime medical records, the hypertension was first noted before the age of 40, the average age of diagnosis being about 38 years for these 26, as compared to 41 years for the whole hypertensive group of World War veterans. The earlier recognition of hypertension in those patients who had wartime illness or injury may be due to more or less continuous observation since their discharge.

Official records of 11 patients were available for diagnoses and treatment rendered before the appearance of clinical hypertension was noted.

One patient was first seen in 1931, at which time he gave a history of life-long headaches. He had taken large quantities of a proprietary analgesic. He was an aviator during the War, had influenza and malaria in 1918 and 1919, since which time he had never felt well. In 1931, his blood pressure was 136 systolic and 86 diastolic, his retinal arteries showed moderate sclerosis, the blood chemistry and urine were normal. In 1933, the blood pressure was recorded between 174 and 200 systolic and 106 and 128 diastolic. In 1935, he died of an intracranial hemorrhage following congestive failure.

The headaches and cerebrovascular changes as shown by sclerosis of retinal arteries preceding the hypertension, suggests a relationship between the intracranial circulatory changes and the hypertension.

The second case was seen in 1931 because of gastrointestinal complaints. His blood pressure during that admission was 138 systolic and 80 diastolic, and definite retinal sclerosis with bilateral neuroretinitis was observed without evidence of renal or cardiac damage. In 1933, he was given a diagnosis of hypertension, and in 1935, the blood pressure was 170 systolic and 110 diastolic. He was admitted for treatment of cardiac failure and showed generalized arteriosclerosis, cardiac enlargement, bundle branch block, normal blood chemistry except for a uric acid of 4.8 mg. per cent, a trace of albumin and occasional hyaline cast in the urine, and normal P.S.P. (phenolsulphonephthalein elimination). This patient was 39 years of age when first observed. His father had died at the age of 31 of "acute indigestion."

In this case again, the changes in the retinal arteries were the first evidence of vascular disease noted and this suggests that the intracranial vascular lesions preceding the clinical hypertension may have been important causally, although generalized vascular sclerosis appeared comparatively early.

The third patient had been seen in various facilities and offices since 1922. During the War, he had had measles followed by otitis media and arthritis which persisted and greatly crippled the patient. In 1926, he was diagnosed dementia precox and possible endocrinopathy. In 1927, an albuminuria was noted; in 1931, an iritis resulting in loss of vision in one eye and partial loss in the other; and in 1932, hypertension. In 1936, his blood pressure was 170 systolic and 110 diastolic, the blood chemistry was normal except for a blood uric acid of 4.2 mg. per cent, and no other evidence of renal disease was found. There was slight cardiac enlargement. The patient still complained of his arthritis, and his mental condition had required institutional care on several occasions.

The severe chronic arthritis and otitis media, the mental illness, and the possible endocrine dysfunction were the important conditions preceding the development of hypertension in this patient.

The fourth patient had been treated in Veterans' Administration facilities since 1923. He had otitis media while in the Service which continued as a chronic sup-

purative otitis media until 1926 when a mastoidectomy was done. This was followed by a thrombosis of the lateral sinus and an extradural abscess in the middle fossa. He had had headaches since the War and in 1931, a retinitis suggestive of hypertension was noted. At this admission, his blood pressure was 120 systolic and 70 diastolic but his urine showed some albumin, casts, and red blood cells. The blood chemistry and P.S.P. were normal. In 1936, the blood pressure was 144 systolic and 96 diastolic, the blood chemistry and P.S.P. were still normal except that the blood uric acid was 4.9 mg. per cent, and the urine showed a trace of albumin and an occasional hyaline cast.

The history of an ear infection persisting for almost 10 years, resulting in an extradural abscess and the evidence of renal involvement with retinal changes may be important.

The fifth patient had been seen in Veterans' Administration facilities since 1919. He had had various diagnoses of hysteria, petit mal, epilepsy and constitutional psychopathic state. During the War, he had rheumatic fever but later saw active service and received a gunshot wound. He was hospitalized on several occasions in mental institutions for psychotic episodes. In 1931, he was observed to have a low grade retinitis with small arteries which showed thickening. The blood pressure at that time was 110 systolic, 90 diastolic, and the urine was negative. In 1934, the blood pressure was 178 systolic, 126 diastolic; the blood chemistry and urine were normal except for a uric acid of 4.9 mg. per cent.

This patient was 37 years of age when hypertension was first discovered and changes in the retinal arteries had been noted three years before. He also had mental illness with psychotic episodes.

The sixth patient, a colored veteran, had been seen from 1922 in Veterans' Administration facilities. He had pneumonia during his service and never returned to duty following his illness. Since 1922, he had been diagnosed pulmonary tuberculosis by some and no pulmonary disease by others. Hypertension was first noted in 1929 when the patient was 36 years of age. In 1936, his pressure was 196 to 220 systolic and 130 to 136 diastolic.

The patient had been very nervous, restless and easily frightened, but no definite cause for his disability prior to the hypertension was found except the sequelae of the pneumonic infection.

The seventh patient had been under treatment since 1919. During the War, he was gassed and claimed to have been shell-shocked, following which he was very nervous with many complaints suggesting neurocirculatory asthenia. He was diagnosed chronic bronchitis, tuberculosis by some and not by others, psychoneurosis by some and not by others. In 1934, he was given a diagnosis of hypertension and nephritis. In 1935, his blood pressure was 176 systolic, 116 diastolic; the blood chemistry was normal except for a uric acid of 4.2 mg. per cent. The urine showed 4-plus albumin, hyaline and granular casts. The P.S.P. was normal.

The diagnosis of nephritis apparently was based on the presence of hypertension and abnormal urinary sediment, without any history of an acute attack. It was felt, at a later date, that this patient did not have a nephritis primarily but showed renal dysfunction secondarily to hypertension. The trauma during the War and the succeeding psychoneurosis are outstanding in the history preceding the diagnosis of hypertension.

The eighth patient had been seen from 1921 in Veterans' Administration facilities. During the War, he was hospitalized with rheumatism of his legs and erythema nodosum. This condition recurred in 1920 and 1933, as well as an otitis media in 1930. He had had diagnoses at various times of diseased tonsils, effort syndrome, and hypertension in 1931 for the first time. In 1935, his pressure was 156 systolic and 108 diastolic. The blood chemistry was normal except for a uric acid of 4.2 mg.

per cent, and the urine was negative. The basal metabolic rate was minus 15 per cent, and he weighed over 200 pounds.

The diagnosis of hypertension was made at the age of 32 years. He had a history of rheumatic infection without cardiac involvement. The comparatively mild hypertension may have been associated with an endocrine dysfunction suggested by the obesity and low basal metabolic rate.

The ninth patient had been seen since 1922 in Veterans' Administration facilities. He was qualified for limited service during the War because of a previous fracture of the left tibia. Since 1918, he had had arthritis requiring bed care for several months of every year. In 1929, a diagnosis of uncomplicated nephritis was made which improved with treatment. In 1934, hypertension was first noted on his record, and in 1936, his blood pressure was 205 systolic, 120 diastolic. There was retinal and peripheral arteriosclerosis. The blood chemistry was normal except for a uric acid of 5.4 mg. per cent, and the P.S.P. was normal. The urine showed a trace of albumin in several specimens and an occasional hyaline cast which was not considered sufficient to make a diagnosis of nephritis.

The recurring chronic arthritis with a fairly high uric acid may indicate that the patient had gout since the other renal findings are no greater than might be expected with a blood pressure of over 200 systolic. This patient was a painter by occupation but gave no history of lead poisoning and he had not worked since 1932.

The tenth case had been seen in Veterans' Administration facilities since 1928 and given diagnoses ranging from psychoneurosis with depression to toxic psychosis. When first observed in the hospital in 1930, his blood pressure was reported as 130 to 142 systolic and 90 to 106 diastolic. He stated that since boyhood he had been "high-strung," resented authority, and wanted to be free and independent. He claims to have been slightly gassed and knocked unconscious by an exploding shell during service and at the time of discharge was very nervous. The diagnosis of psychoneurosis, moderately severe, has been continued up to the present.

This patient presents a tense mental reaction without other evidence of organic illness as a possible explanation of his hypertension.

The eleventh patient, a dentist, had been seen as a patient in Veterans' Administration facilities since 1924. In November 1924, he was examined for a Reserve Commission, at which time the blood pressure was reported as 130 systolic and 87 diastolic, heart and arteries normal. Later in the same year, he was given a diagnosis of mitral stenosis which was repeated on several occasions subsequently, as well as the diagnosis of neurasthenia; but in 1936 there was no evidence of heart disease. Hypertension was first noted in 1929. The patient dates his symptoms to the bombing of the hospital in which he was on duty in France, and injury to his head when thrown by the force of the explosion. Since then, he claims that he has been a changed person and has not been able to practice because of his nervous tremor and tension.

There is very little in this patient's history except the long-standing neurasthenia and possible cranial trauma to account for his hypertension. The neuropsychiatric consultant made a diagnosis of cerebral arteriosclerosis apparently on the basis of his mental reactions.

In this group which had been under observation for 5 to 17 years prior to the last admission to the hospital, the medical histories are very dissimilar. Four had had arthritis of various types, three had had otitis media, one with mastoiditis and extradural abscess, one had had pneumonia, one influenza, and one malaria. There were no histories of acute nephritis in this series. The histories of infections during Service are not much different from what might be expected in a civilian population, and the cases are too few to

demonstrate any relation between specific infections and hypertension. Only one patient in this series developed tuberculosis during the War and this one was a female whose hypertension appeared many years after her pulmonary condition was quiescent. Several others were suspected of having tuberculosis but the later course would indicate that this was not the case.

Syphilis has frequently been cited as a causative factor in essential hypertension although this is denied by most authors in recent years. Among the patients who had hypertension, eight had positive blood Wassermann reactions, one a positive Kahn reaction and negative Wassermann and six gave definite histories of syphilitic infection although their blood Wassermann reaction was negative while in the hospital. Fifteen patients, all of whom were males, is an incidence of approximately 18 per cent. A diagnosis of syphilis on the basis of a positive Wassermann reaction only was made on 64 of the whole discharged group or approximately 5 per cent. The incidence of syphilis among the hypertensives is greater even if only Wassermann positive cases are considered, but it is perhaps most important that 11 of the 15 patients or 73 per cent were colored, which is 65 per cent of the total number of colored patients with hypertension. Among the white patients with hypertension, the occurrence of syphilis does not vary significantly from the general incidence. In the Negroes, syphilitic infection if not the basic cause of hypertension, may account for the early development and the severe forms with frequent vascular accidents.

In four of the preceding patients, examination of the retina revealed sclerosis of the vessels several years before hypertension was noted clinically. It has been postulated before that vascular lesions in the brain [3] are responsible for many instances of hypertension although Cutler [4] has offered considerable negative evidence to the contrary. The presence of cerebral arteriosclerosis as indicated by changes in the retinal arteries, before the development of any definite elevation of blood pressure, however, would further suggest the importance of cerebral vascular changes in the causation of essential hypertension.

At least four patients gave histories of cerebral trauma from falls or explosions in their immediate vicinity. One also had done considerable deep-sea diving without decompression which is said to frequently cause intracranial vascular changes. The possibility that cranial trauma may cause brain lesions, resulting in chronic hypertension in some cases, is suggested. It is unlikely that this could be proved by histological studies in view of the limited knowledge of central control of vasomotor centers and the anatomical pathways involved.[5]

Neuropsychiatric Conditions

In the group under study who exhibited hypertension, 11 patients were given diagnoses of organic and functional mental disease of various kinds. Five were classified as having dementia precox, one paresis, one senile

psychosis and four severe psychoneurosis. Several others complained of psychoneurotic symptoms of more or less severity, but the above four developed their illness during the War. The influence of chronic anxiety states and other mental illness on the development of chronic hypertension can only be surmised, but it is true that these conditions are present in many cases before the blood pressure becomes chronically elevated. The effect of emotion in raising the blood pressure acutely is commonly observed and the "high pressure," "quick-tempered," individual not infrequently has hypertension.

As an indication of psychoneurosis, it is interesting that at least eight of the hypertensive patients were addicted to the use of alcohol in large quantities. Thirty-one admitted the moderate use of alcohol and 24 did not use it.

Obesity

In the series of 82 patients with hypertension, 24 gave a history of obesity in the past or at the time of their admission. These patients had at some time weighed over 200 pounds, which for most individuals is definitely above normal. The age, weight and sex were not considered in this classification but a comparison was made with the incidence of individuals weighing 200 pounds or over, at some time in their life, in a group of 80 patients who had diagnoses of benign tumor, cardiac neurosis and urticaria. None of this latter group suffered from hypertension or wasting illness and only four weighed over 200 pounds. The frequent occurrence of hypertension among obese individuals has often been observed although the mechanism or significance of the relationship cannot be explained.

Endocrine disturbance is often present in both conditions and one of our patients presented a fairly typical picture of a Cushing syndrome with obesity, hypertension and diabetes. Three other patients had diabetes, two of whom were obese while the third was not. The latter patient was 71 years of age and had a comparatively mild diabetes. Hypertension has been reported occurring frequently in diabetes but diabetes is present in only a small percentage of hypertension patients.[6, 7]

Heredity

Information regarding the illnesses of other members of a family is rarely sufficiently complete or accurate to draw definite conclusions concerning the hereditary influence involved in any particular type of illness; the colored patients, especially, often know very little about their parents or their brothers and sisters. Fourteen records did not contain any statement regarding either parent. However, of these patients, 10 were over 60 years of age themselves. The age of the parents at death was shown for 48 fathers and 47 mothers, the average being 65 years and 60 years respectively. The fathers of seven patients were still living and their average age was 73

years, while 13 mothers were still living with an average age of 69 years. In a few other instances, the ages of the parents were not known, but it is likely they would only have raised the average age as the statements were made that they died of old age or were old and feeble. These figures would indicate that the males survived the females by several years and that the longevity of the parents of these patients with hypertension was well up in the normal range of life expectancy. Practically all of the deaths of parents in earlier life were due to acute infections, accidents and child-bearing, and only four deaths before the age of 60 were from heart disease.

At least 37 of the veterans had one member of their family, composed of their parents and siblings, who had died or were suffering at that time from some form of cardiorenal-vascular disease, the most common being a cerebral accident. Fourteen of these were in brothers and sisters below the age of 60. Eleven families had two members, and four families three or more members beside the veteran patient, with cardiovascular-renal disease.

Compared to a group of 80 non-hypertensive patients, the proportion of parents whose age at death was known in both groups was about the same and the average age at death was several years greater in the parents of the hypertensive patients. The age of a few more of the living parents of non-hypertensive veterans was given than in the other group, but here again, the average age is somewhat greater in the parents of hypertensive patients (table 2).

TABLE II

Parents of Veterans

		Fathers				Mothers			
	No. Patients	Dead	Av. Age Death	Living	Av. Age	Dead	Av. Age Death	Living	Av. Age
Hypertension	82	48	65	7	73	47	60	13	69
Non-Hypertension Control	80	46	62.8	16	70	41	55.4	16	66

There is a definitely greater incidence of cardiovascular-renal disease in the immediate families of hypertensives than in the non-hypertensive group as indicated by the table (table 3). It is suggestive also that 22 members of the families of the hypertensive patients had had strokes, apoplexy or

TABLE III

Number of Families with Cardiovascular Disease in Other Members than Patient

	Hypertension	Non-Hypertension Control
One other member	37	21
Two other members	11	4
Three or more other members	4	1

paralysis while only three relatives of the non-hypertensive patients had had such conditions as indicated by the records.

Twenty-one patients were given a diagnosis of hypertension before the age of 40 and of these, there was at least one other member of the family with cardiovascular-renal disease in nine. This is about the same proportion as in the whole group.

The family history of the patients that died showed a high incidence of cardiovascular-renal disease in six, and the other two did not give adequate histories.

It is reasonable to suppose that constitutional factors, familial reaction patterns, and habits of living are of some moment in the development of hypertension. This study is suggestive of this influence as indicated by the greater incidence of cardiovascular-renal diseases in the families of patients with hypertension as compared to a non-hypertensive group although the longevity of the parents favored the former. Even those parents who died of cardiovascular-renal disease were on the average above 60 years of age, and not infrequently the statement was made that the parents were over 70 or 80 when they died of a stroke.

Occupation

The occupation record was given quite completely in all cases except 10 which included those veterans who had not worked since discharge from service and those who had retired many years previously because of age or disability. Five groups were separated on the basis of the physical work involved in their occupation: 1, clerical work; 2, salesmen and shopkeepers; 3, professional people including doctors, dentists, lawyers, nurses, and army officers; 4, heavy laborers such as farmers, blacksmiths, machinists, laborers, etc.; 5, light laborers such as carpenters, painters, housewives, chauffeurs, etc. It obviously is impossible to accurately classify physical effort so dogmatically, but the following distribution with the average age is presented and attention is directed to the low average age of the salesman group and the comparatively higher average age of the clerical and professional groups as compared to the laboring groups. The rather high percentage of the professional class in this series from a general service hospital suggests a high frequency of hypertension in individuals in such occupations (table 4).

Table IV

Occupation and Hypertension

	Class	No. Patients	Per cent	Av. Age at Obs.
Clerical	1	10	12.2	52.1
Salesmen, etc.	2	12	14.6	44.4
Professional	3	13	15.8	54.7
Heavy laborers	4	18	21.9	49.6
Light laborers	5	19	23.1	46.7
Unclassified	6	10	12.2	56.9

It is impossible to say from the records whether the individuals in the salesman group were high pressure types or not. It seems more likely that they were men with some physical handicap for which they sought treatment earlier and who chose an occupation permitting some irregularity of attendance.

As would be expected from such a hospital population, the laboring groups are the largest. Speculation as to the significance of the younger average age is covered in the next section.

Cardiac Enlargement

In many instances, the 82 patients exhibiting hypertension were admitted to the hospital primarily for treatment or study of other conditions. Thirty-four were found to have no objective evidence of heart disease and in six patients with hypertension, the cardiac involvement was considered to be principally of syphilitic etiology.

The average age of the hypertensive patients without heart disease was 49.5 years, only slightly less than the general average for the whole group. Thirty-nine patients were considered to have cardiac enlargement and their average age was 51.5 years. As far as could be determined from the histories given by the patients and the previous records, the patients with cardiac enlargement had been diagnosed hypertensive an average of four years before their present admission, while in the whole group, the presence of hypertension had been known on an average of nine years.

When the incidence of enlargement in the various occupational groups was compared with their proportion of the whole group, it was observed that the heavy laboring group was responsible for the largest percentage with cardiac enlargement, definitely greater than the per cent of this class in the whole group. The salesman and shopkeeper group also showed a higher percentage with cardiac enlargement than would be expected from their representation in the group. Excessive exertion might be expected to contribute to cardiac enlargement but such an explanation is hardly applicable to the salesman group which also showed a low age at the time of observation.

Twenty-six per cent of the patients with enlarged hearts were colored while approximately 21 per cent of the hypertensive group were colored, indicating not only a high incidence of hypertension but also a high per cent with cardiac involvement. The facts that the colored veterans were largely engaged in laboring occupations and that 65 per cent of them had syphilis are undoubtedly important for the explanation of this racial tendency to cardiac involvement.

All the patients with mean pressures above 170 mm. Hg had cardiac enlargement. Most of the patients with comparatively low mean pressures also showed cardiac enlargement but their histories and electrocardiograms indicated previous attacks of coronary occlusion or hemiplegia.

Thirty-eight per cent of the patients with enlargement also weighed or had weighed over 200 pounds. Thus 60 per cent of the obese patients were in this group comprising about 18 per cent of all the hypertensive patients. Due allowance for the difficulty in determining heart size accurately in such patients should be made in interpreting this relationship.

In the development of cardiac enlargement in hypertensive patients, the height of the mean pressure, the type of occupation, syphilis, and possibly obesity were probable factors (table 5).

TABLE V

Occupation and Cardiac Enlargement

	Class	Incidence of enlargement Per cent	Incidence in series Per cent
Clerical	1	7.7	12.2
Salesmen, etc.	2	17.9	14.6
Professional	3	12.8	15.8
Heavy laborers	4	30.7	21.9
Light laborers	5	15.4	23.1
Unclassified	6	12.8	12.2

ELECTROCARDIOGRAMS

In 48 of the 82 cases, electrocardiograms were reported. Of these, 23 were within normal limits. Six showed only left axis deviation as an abnormality and 19 presented definite abnormalities. The most common finding was inversion of the T-wave in Lead I, which occurred nine times, in three instances associated with inversion of the T-waves in the other two leads, and in one instance, with an inverted T_2 only. Inversion of the T-wave in Leads II and III occurred five times each, but coincided only the three times previously mentioned when all the T-waves were inverted.

The voltage of T-waves was reported low (less than 0.1 millivolt) four times in Lead I, six times in Lead II and three times in Lead III.

The QRS voltage was reported to be less than 0.5 millivolts in all leads in three cases. In the tracing of one of these patients who had had myocardial failure for several years, the QRS complexes were W-shaped and death occurred during his admission. The other two patients had blood pressures that were comparatively low and questionably abnormal. They both had numerous complaints which did not include cardiac pain.

High voltage tracings have been described as more characteristic of hypertension [8] but none were observed in this series. Low voltage QRS complexes apparently were not related to uncomplicated hypertension.

Three tracings showed deep Q_3 waves which satisfied the usual criteria for significance.[9] One of the patients gave a history of a severe attack of pain about 10 days before his admission, and his electrocardiogram presented changes suggestive of a healed anterior coronary occlusion and an

acute posterior occlusion. A second patient had a history of precordial pain with cardiac insufficiency for three years preceding his admission and showed also a negative T_3 without left axis deviation or definite cardiac enlargement. It is probable that this patient also had had a coronary occlusion in the posterior portion of the heart. The third patient had had a very high pressure for a number of years, but in this case, the deep Q_3 with an inverted T_3 and left axis deviation may have been the result of a transverse position of the heart in the thorax.

One patient exhibited bundle branch block and one auricular fibrillation. One of the fatal cases showed a coronary occlusion at autopsy and two years previously his electrocardiogram had shown inverted T-waves in Leads I and II. Another patient gave a suggestive history of precordial pain two months before admission and his electrocardiogram showed inversion of T_1 with low voltage of T_2 and T_3. While only one patient died from an acute coronary thrombosis, the history of several others with their subsequent clinical course, suggested that they had experienced acute attacks probably involving the posterior portion of the heart or small vessels. In any event, characteristic electrocardiographic abnormalities which might not be due to coronary artery disease were not seen in this series.

Blood

Polycythemia is sometimes associated with hypertension, and in certain cases the increased viscosity of the blood which results from the increased number of cells may at least be an added factor increasing peripheral resistance. A recent case, not included in this series, exhibited a marked decrease in mean pressure with relief of symptoms when the red blood cells were reduced in number.

When the blood counts of the patients in this series with hypertension were compared with those of a similar sized group of hospital patients without hypertension, the latter group had a greater number with hemoglobin above 16 gm. per 100 c.c. or red blood cells above 5,000,000 per cu. mm. than the hypertensives. True polycythemia occurred only once in the hypertensive series and the incidence of this condition as a causative factor in hypertension cannot be great. It might be expected that a secondary polycythemia would develop, particularly in those patients with much arteriosclerosis involving pulmonary vessels, but this was not the case, perhaps because of the age group involved.

Anemia may be observed in patients with hypertension, particularly those associated with or due to renal disease. In this series, 31.2 per cent of the patients had a hemoglobin content of less than 14 gm. per 100 c.c. in their blood, while in the control group, the percentage of patients with a hemoglobin below 14 gm. per 100 c.c. was 21.3 per cent. Only eight of the 25 hypertensives with some degree of anemia had manifestations of kidney dysfunction, principally albuminuria and cylindruria (hyaline casts); micro-

scopic hematuria having been reported only once and an elevated N.P.N. (non-protein nitrogen) three times.

Renal Function

The association of renal disease with hypertension is commonly observed but the etiological relationship of one to the other is usually obscure. Unless there is a history of an acute nephritis or some other renal condition such as polycystic kidney, the signs and symptoms of renal involvement seem to follow the development of hypertension.

The recent investigations of Goldblatt et al.[10] and of Wood and Cash[11] demonstrate that hypertension of varying degrees of severity may be produced in dogs by constriction of the renal arteries without causing apparent loss of renal function. It is possible that a mild involvement of the kidneys occurs in man which may not affect the function or cannot be detected by our clinical methods, but is sufficient to cause an elevation of blood pressure. At present, such a hypothesis would probably involve a chemical factor causing generalized constriction of the arterioles, and confirmation of such an etiological theory in human beings has been and will continue to be confronted by many technical difficulties and opposing data.

In this series, only two patients gave a history of an acute renal involvement preceding or accompanying the hypertension, one an acute nephritis, and the other a pyelonephritis with obstructing renal calculi.

Various tests of renal function were performed on 56 of the 82 patients and while some show changes which were interpreted as indicating renal dysfunction, not infrequently the kidney failure has been secondary to congestive heart failure. In these cases, if the patient regained his cardiac compensation, the renal function became normal.

In a control group of 63 hospital patients not exhibiting increased blood pressure, the N.P.N. was reported to be greater than 35 mg. per cent in 11 or 17.4 per cent, and of these, two had definite arteriosclerosis, one died of a coronary occlusion, one had chronic nephritis and the remainder had other severe systemic illnesses. Determinations of the N.P.N. were reported for 56 of the hypertensive patients, and of these, 14 or 25 per cent were above 35 mg. per cent. The highest value was 88.3 mg. per cent for a patient who gave a definite history of renal obstruction. It appears that an elevated N.P.N. occurs comparatively infrequently in hospital patients who do not have hypertension or other evidence of cardiovascular involvement.

The blood uric acid was reported on the same patients in the two groups; 44 per cent of the hypertensives had a blood uric acid of 4 mg. per cent or above, as compared to 27 per cent in the control series. As indicated in the table (table 6), this is due largely to the number of hypertensive patients with a slight increase in the concentration of uric acid (from 4 to 5 mg. per cent) and the disproportion would be even greater if the patients with heart disease as well as the hypertensives were excluded from the control group.

TABLE VI

Blood Uric Acid in Patients with and without Hypertension

Uric Acid mg. per cent	Hypertensives per cent	Control per cent
4–5	32.1	17.4
5–6	5.1	7.9
6–7	1.8	1.6
7–8	5.3	0

About half of the hypertensive patients with elevated uric acid did not show any other evidence of renal disease as indicated by the non-protein nitrogen, phenolsulphonephthalein elimination, specific gravity, microscopic examination, and albumin. The four patients with a uric acid above 6 mg. per cent also had N.P.N's. above 35 mg. per cent, but only five of the 21 with uric acids between 4 and 6 mg. per cent had elevated N.P.N.'s. Five of the nine cases in which both the uric acid and N.P.N. were elevated died, but in only one of these was death preceded by uremic symptoms and the others represented advanced cardiac failure.

Nine of the 14 patients with N.P.N. above 35 mg. per cent had uric acids above 4 mg. per cent, five being above 5 mg. per cent. This suggests that an elevation of the blood uric acid occurs more frequently in hypertensive renal insufficiency than an elevation of the N.P.N. and the two values do not necessarily vary together. In the control series, only three patients out of 46 with a blood uric acid of less than 4 mg. per cent had N.P.N.'s. above 35 mg. per cent, while seven out of 17 patients with blood uric acid above 4 mg. per cent had N.P.N.'s above 35 mg. per cent. The magnitude of increase in either value was not necessarily reflected in the other, thus the highest N.P.N. which was 63 mg. per cent was accompanied by a uric acid between 4 and 5 mg. per cent, and the highest uric acid concentration, between 6 and 7 mg. per cent, was obtained in a patient with an N.P.N. of only 38.9 mg. per cent. The uric acid concentration frequently is increased without other evidence of renal dysfunction and in conditions which are not commonly associated with renal damage. When the concentration was elevated in patients with hypertension, it probably indicated decreased kidney function and when higher concentrations occurred, the prognosis was unfavorable. Five of seven hypertensives with uric acid above 5 mg. per cent died and the other two had evidence of recent coronary occlusions which they survived. The N.P.N in both of these latter cases was normal and it is suggested that the hyperuricemia was extra-renal in origin. Dependence on the estimation of the retention of one chemical substance in the blood is obviously very unsatisfactory for detecting a reduction in renal function in hypertension.

The elimination of phenolsulphonephthalein injected intramuscularly in two hours was estimated in most of the control series along with uric acid

and N.P.N. In only one case out of 16 in which the uric acid was above 4 mg. per cent, was the P.S.P. below 40 per cent. This method of performing the examination apparently gives very little information in lesser degrees of renal failure.

The highest specific gravity reported for any specimen of urine during the patient's stay in the hospital was recorded. In 11 cases the specific gravity was less than 1.020 but in five of these, no albumin or abnormal findings in the urine sediment were reported. Six showed varying amounts of albumin, three showed hyaline and granular casts and two showed some nitrogen retention in their blood.

In the control group, the urine of only nine out of 76 patients showed a specific gravity below 1.020. Five of these had hypertension or arteriosclerosis, three had albuminuria and two moderate nitrogen retention. The opinion has frequently been expressed by other investigators that concentration tests are of particular value in evaluating kidney function, but good cooperation on the part of the patient is essential. In our experience, this is not always obtained on general wards that can not be closely supervised.

Twenty-one in the hypertensive group showed varying amounts of albumin in their urine with a specific gravity of more than 1.020. No attempt was made to correct for the albumin.

Routine determinations of urea or creatinine clearances were not made in this series. It is generally conceded that such studies are of more value than single estimations of one of the nitrogenous blood constituents but even the clearances are subject to wide variations and require considerable supervision. The routine performance of various laboratory examinations by technicians without proper evaluation by the clinician of the conditions under which the examination was made or the proper control of the patient may give data that are more confusing than helpful. A limited number of well conceived, properly performed procedures are of more value in the general study of a patient with hypertensive heart disease than many random examinations less carefully controlled.

Deaths

In this small series of hypertensives, there were only eight deaths, or a mortality of 9.7 per cent, with an average age at death of 53 years as compared to the whole discharge group in which there were 91 deaths or a mortality of 5.6 per cent and an average age at death of 52 years. In this latter group, the average age at death of the colored patients was 46 years and of the white patients 53.8 years.

One of the patients, aged 42 years, had had headaches all his life as had his mother. During the War, he was an aviator but did not go overseas. He had malaria from 1919 to 1922 and had not felt well since. In 1931 when first examined, his blood pressure was 138 systolic, 86 diastolic, his retinal and peripheral vessels showed some thickening but there was no evidence of renal or heart involvement.

In 1933 his blood pressure was 200 systolic, 128 diastolic. His headaches were more frequent and associated with nocturia.

In 1935 he was admitted to the hospital with congestive heart failure which improved. His blood pressure was 215 systolic and 140 diastolic. The N.P.N. was 43.7 mg. per cent on admission but dropped to 33.3 mg. per cent as the signs of heart failure disappeared. About one month after admission, he was feeling very well when he suddenly complained of a sensation of acid being poured over his face and left side. He soon developed unconsciousness and died.

The postmortem examination revealed a small hemorrhage in the pons, and unusually marked sclerosis of the vessels of the Circle of Willis. The heart showed hypertrophy of the left ventricle with a small area of healed infarction. The kidneys were about normal in size, the larger vessels showed sclerosis, the glomeruli were large and some showed hyalinization.

The second patient, aged 64, was admitted in an unconscious state and died within 72 hours. A history was not obtained but he presented evidence of a right-sided hemiplegia with a hypertension of 178 systolic and 120 diastolic. The blood N.P.N. was 70.5 mg. per cent, uric acid 7.9 mg. per cent and the urine showed a few red blood cells, many hyaline and granular casts and 1-plus albumin.

The postmortem examination failed to reveal a localized cerebral lesion of any kind but the brain and ventricles were filled with fluid resembling the so-called alcoholic wet brain. The cerebral vessels were definitely sclerotic. The kidneys were somewhat small with adherent capsules and decreased cortical width. Certain areas showed fibrosis with complete obliteration of the glomeruli while others were distended. The heart was enlarged and showed swelling of the muscle fibers with considerable interfibrillar connective tissue. Death apparently was due to renal failure.

The third patient was 45 years old and colored. He had worked as a laborer until a few weeks before his first admission in 1933 at which time he had congestive heart failure. The highest blood pressure obtained during his hospitalization was 148 systolic and 105 diastolic. His renal function was good. He was admitted in extremis about two years later and at autopsy the heart was enlarged and presented a saucer-like fibrous dilatation near the apex and a fresh mural thrombus beneath an area on the left ventricular wall in which the musculature was necrosed and infiltrated with polymorphonuclear cells. The kidneys were small and contracted showing cellular infiltration and intertubular fibrosis. The larger vessels were definitely sclerotic and an occasional glomerulus was obliterated.

The fourth patient was a Spanish-American War veteran, 66 years old. He had had a diagnosis of high blood pressure and heart disease for many years but had been able to work as a steam engineer until three months before his admission. He gave a history of a recent intestinal hemorrhage which had resulted in a profound anemia and apparently heart failure.

The postmortem revealed no tumor of the gastrointestinal tract but an area near the splenic flexure with many bleeding points from distended veins. The aorta above the sinuses of Valsalva down to the iliac bifurcation was the site of a severe arteritis with loss of elastica, irregular fibrosis, ulceration, hemorrhage into the wall with fatty change, and calcareous plaque formation. The heart showed fragmentation, swellings and granularity of the muscle fibers. The kidneys showed dilated tubules filled with detritus with focal reaction and fibrosis about some glomeruli, although the tubular involvement was the most striking. The liver showed a perilobular round cell reaction and evidence of cell degeneration which was called an infectious hepatitis. There was a small adenoma in one adrenal. It was felt that death was due to an infectious aortitis with the intestinal hemorrhage as contributory.

The fifth patient was a World War veteran, aged 45. His only illness during service was trench mouth and he had been well since discharge until 1929, when he

had had kidney stones for which he was cystoscoped. It is not known what his blood pressure was then or the exact location of the stones, but from that time he had not been well. In 1935 he was treated in another hospital for nephritis and subsequently in this hospital where he died. Because of the high blood pressure, evidences of renal insufficiency and cerebral symptoms, a diagnosis of uremia was made. Postmortem examination was refused but this case was considered to be a chronic nephritis with secondary hypertension and uremia.

The sixth patient was 74 years old and had served as a Medical Officer during the World War. He was admitted because of senile psychosis and congestive heart failure, apparently dying of bronchopneumonia. Postmortem examination revealed the usual changes of arteriosclerotic heart disease in the heart, blood vessels and kidneys.

The seventh patient was a World War veteran, aged 45. He had known of his hypertension for at least five years and recently had complained of marked cardiac insufficiency. He was semi-stuporous when admitted, had an extremely high blood pressure with papilledema and numerous areas of retinal exudate. Kidney function as evidenced by the blood chemistry and urinary findings was normal. This was considered a malignant hypertension with cerebral edema. Postmortem examination was not permitted.

The eighth patient was a World War veteran, aged 41. He had had scarlet fever, diphtheria and empyema in early childhood, typhoid fever at age 15, and during the War received a gunshot wound and a burn with liquid fire. He was also confined in a German prison camp for four months during which time he first noticed dyspnea and edema. Since discharge from the Army, he had been able to do some work as a salesman until about 1928, but always had some cardiac insufficiency. On admission to the hospital in 1934, he was in severe congestive heart failure and made very little improvement during his 18 months hospitalization. Although he presented evidence of renal insufficiency, this was considered a result of his myocardial failure. An autopsy was not performed. The diagnosis was hypertensive heart disease with congestive failure.

Three of the patients, therefore, were over 60 years of age; one died of bronchopneumonia with congestive heart failure, one apparently died of uremia while the third died following severe intestinal hemorrhages and had a marked aortitis, probably infectious in origin. The remaining five patients were between 37 and 47 years of age at the time of their death and a common factor that may have been responsible for their severe and comparatively short course is not apparent. The immediate family histories indicated a fairly high familial tendency to cardiovascular disease. Renal injury appears to have been an early factor in one case while marked cerebral vascular changes may have been important in two other cases. Only one patient died of an intracranial vascular accident. The two patients that died of congestive heart failure presented evidence of myocardial damage from coronary artery disease.

Summary and Conclusions

The incidence of hypertension in 1369 veterans was 6 per cent.

There was a comparatively greater incidence of hypertension among the negro patients whose average age was about five years younger than that of white patients.

A high proportion of the negro patients have syphilis which may account for the early and more serious involvement.

The morbidity history during service and subsequently, did not implicate any particular infection as a precursor of hypertension.

Involvement of the retinal arteries with a sclerotic process was observed four times before the blood pressure became chronically elevated. This suggests involvement of the cerebral circulation as a factor in the causation of some cases of hypertension.

Psychotic and severe psychoneurotic manifestations were found in 13 per cent of the cases. Four patients had suffered cerebral trauma. It is suggested that certain chronic emotional reactions and brain injuries may influence the central regulation of blood pressure.

About one-third of the patients with hypertension had been obese at some time in their lives as evidenced by body weight over 200 pounds.

A definitely greater incidence of cardiovascular-renal disease was reported in the immediate families of hypertensive subjects than in a control group.

The more laborious physical occupations were the most common means of livelihood for about 45 per cent of the group, and the average age of the patients was lower than the professional and clerical groups.

Cardiac enlargement was apparent in about one-third of the patients. The height of the mean pressure, occupation, syphilis, and possibly obesity, were the most prominent factors associated with enlargement.

Typical electrocardiographic changes that are not characteristic of coronary artery disease were not noted.

Polycythemia was present in only one hypertensive patient while one-third showed some degree of anemia.

Examination of renal function in 56 patients revealed abnormalities of one or more findings in approximately 60 per cent of the cases. A slight rise in the blood uric acid occurred most frequently.

There was very little correlation between the uric acid and the non-protein nitrogen values.

Congestive heart failure was frequently responsible for renal failure.

Death occurred in eight cases or approximately 10 per cent.

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CASE REPORTS

TULAREMIC MENINGITIS

Report of Case with Postmortem Observations *

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The histopathology of tularemia is adequately described in the literature notwithstanding the few reports of postmortem examinations. But because there are few reported necropsies the pathology of the disease is of particular interest in regard to the distribution of the lesions. Last year Bernstein was able to collect only 18 necropsies and to these he added three of his own. We have reviewed these cases and three additional reports by Beck and Merkel, Amoss and Sprunt, and Kavanaugh to determine the distribution of the lesions. This study was prompted by the occurrence of a fatal case of tularemia which was diagnosed at autopsy, and in which the outstanding feature was meningitis. Because there is only one report that describes the pathology of tularemic meningitis and furthermore because in our case lesions were observed in organs where they have not been previously observed, this case is of unusual interest.

Case Report

A negro girl, aged 12, was admitted to the hospital on the third day of her illness. The history was obtained from the father who had been separated from his daughter and it is therefore brief and incomplete. No reason for the lesion on the forearm could be obtained.

The present illness began with fever, abdominal pain and headache, followed by nausea and vomiting 24 hours later. The patient appeared very ill, was semiconscious and the skin was hot and dry. Temperature was 105.8° F., pulse 106, and respirations 24. Blood pressure was 140 systolic, 100 diastolic. The lips were parched and the tongue furred in the center and glazed at the margins. Pharynx and tonsils appeared congested. Impaired resonance was elicited over the right pulmonary apex and scattered râles were heard at the right base. The abdomen was distended, tympanitic and diffusely tender, especially over the cecum and spleen. On the flexor surface of the left forearm near the wrist was an ulcer 3 cm. in diameter, which was surrounded by several small vesicles. The reflexes were normal. The clinical impression was typhoid fever.

Pyrexia was continuous during the eight days of observation, between 103 and 106.2° F., pulse increased from 106 to 160 and respirations from 26 to 40. Culture of the throat proved negative for diphtheria, two stool cultures failed to reveal the *Bacillus typhosus* and the Widal reaction was negative. Total leukocyte count was 8,700, with polymorphonuclear leukocytes 65 per cent, small lymphocytes 33 per cent and large lymphocytes 2 per cent. The red blood cell count was 4,100,000 and the

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hemoglobin estimated at 85 per cent. The tuberculin skin test was negative. On the fifth day of hospitalization the neck was stiff and Brudzinski's and Kernig's signs became positive. The following day semiconsciousness was followed by coma. The abdomen became rigid. Tuberculous meningitis was now thought to be a possibility, although the diagnosis of typhoid was not relinquished and an intestinal perforation was considered. The cerebro-spinal fluid revealed 114 cells per cu. mm., was under 18 mm. Hg pressure but yielded negative tests for globulin. The Wassermann reaction on the spinal fluid was negative. The next day the cell count was 200 and the pressure 22 mm. Hg. Prolonged search in films from both specimens failed to reveal tubercle bacilli. Blood and spinal fluid cultures remained sterile and the blood serum failed to agglutinate the organisms of undulant fever. Coma continued and death occurred the eighth day of hospitalization, or the tenth day of her illness.

Necropsy

A necropsy was performed nine hours after death.

The body was that of a wasted negro female child. An ulcer 3 cm. in diameter with a necrotic base was observed on the palmar surface of the left forearm just above the wrist. In the pia-arachnoid innumerable minute yellow foci were regularly distributed but barely visible over all surfaces of the brain. The cerebro-spinal fluid was yellowish. The cord was not examined.

The peritoneal cavity contained about 400 c.c. of clear light yellow fluid. A small amount of fibrinous exudate was seen on the serosa of the appendix, otherwise the peritoneal surfaces were smooth and glistening. The right pleural cavity contained some 25 c.c. of turbid fluid and the surfaces were dull and congested. The left pleural cavity contained a like amount of clear fluid and the surfaces were smooth and glistening. In the middle anterior part of the upper lobe of the right lung a firm airless area about 5 cm. in diameter was palpated. This, on section, was wedge-shaped, granular and pink but the central part 1 cm. in diameter was yellow and caseous. Otherwise both lungs were alike. They were heavy and soggy but crepitant. Cut surfaces were wet, yielded much frothy fluid and were mottled with slightly raised reddish areas, more numerous in the right lung. The mucosa of the trachea and bronchi was congested. The tracheo-bronchial lymph nodes were enlarged to 2 cm. in diameter and an occasional small yellow focus was seen against the moist gray background.

Through the capsule of the liver, especially near the inferior border, numerous minute yellow areas were visible and a few similar foci were seen on the cut surface. The spleen was a little enlarged, weighing 130 grams. Its capsule was studded with numerous yellow spots. Similarly the cut surface was studded with round yellow foci, the largest about 0.3 cm. in diameter. The mucosa of the appendix in its distal third was necrobiotic and ulcerated. The lymph nodes of a group near the cystic duct were slightly enlarged and several contained small caseous foci. Some three or four left axillary lymph nodes had attained a size of 2 cm. in diameter each and were filled with caseous areas, the largest 1 cm. in diameter. No noteworthy changes were noted in the other viscera.

Microscopic Examination

The floor of the ulcer of the forearm showed necrosis which involved the subjacent subcutaneous tissue. In the necrotic material shadows of macrophages were seen. The tissues immediately around the area of necrosis were infiltrated with de-

generating polymorphonuclear leukocytes and lymphocytes. Ten representative sections from the brain were studied. In the extreme cortex of the cerebrum and in the submeningeal part of the pons there were numerous minute, rather wedge-shaped collections of small round mononuclear cells and an occasional polymorphonuclear leukocyte. Centrally in the foci was much nuclear and cytoplasmic detritus. The small mononuclear cells displayed pyknotic nuclei. The cytoplasm while generally scant was occasionally increased and foamy, thus suggesting microglial origin. The brain tissue around the foci was slightly rarefied. Many of these aggregates were

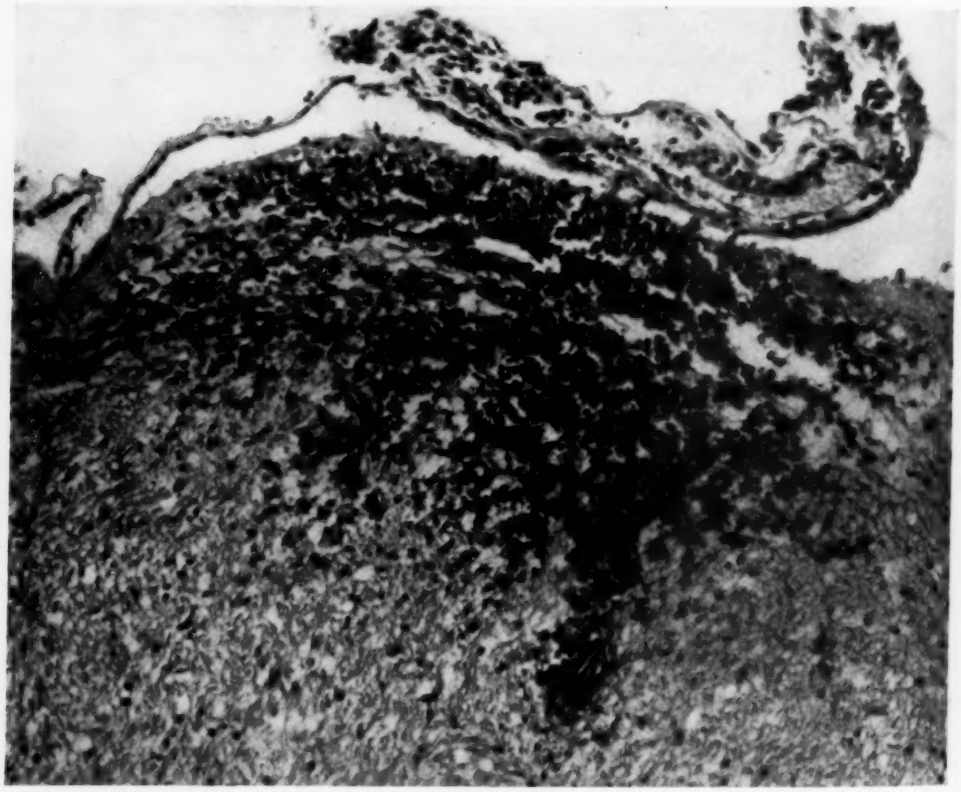

FIG. 1. Section from meningeal surface of pons. Note the wedge-shaped area infiltrated with small mononuclear cells. This focus is confined within the substance of the brain; however, there is a diffuse meningitis. × 240.

confined within the substance of the brain, but the larger ones extended into the leptomeninges. (Figures 1 and 2.) The leptomeninges were furthermore diffusely infiltrated with small round cells and polymorphonuclear leukocytes. A tendency to focal coagulation was noted in the infiltrate. The exudate in the meninges extended a short distance along the vessels into the submeningeal tissue. Beneath the ependyma of the lateral and fourth ventricles smaller foci similar to those of the cortex and pons were found. The ependyma remained intact. Endothelial swelling and proliferation were noted in some of the vessels nearby. No lesions were observed deep in the

brain. The diffuse infiltration of the meninges was noted between the folia of the cerebellum and here and there were deposits of coagulated serum. Slight rarefaction of the submeningeal part of the cerebellum occurred, but no inflammatory foci were seen. In the choroid plexus there was nothing noteworthy.

In the thymus reticular-cell hyperplasia and occasional giant cell formation were noted. The airless area in the right lung was caused by a pneumonic infiltration. The alveoli were filled with fibrin which enmeshed a few large mononuclear cells, lymphocytes and nuclear detritus. Caseous necrosis of the lung and exudate occurred centrally. Similar scattered smaller areas and many necrobiotic areas of local hemor-

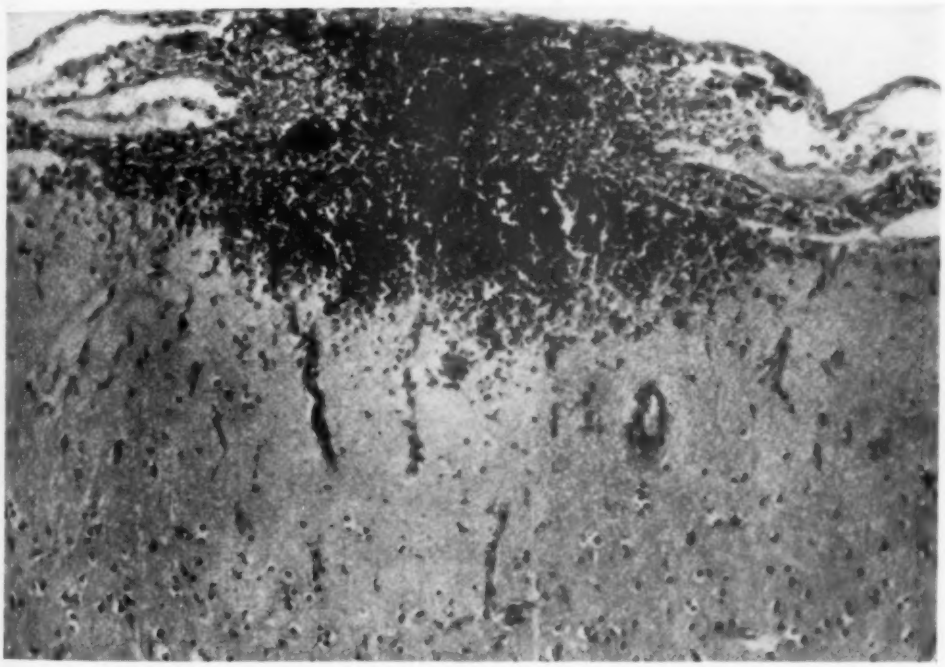

FIG. 2. Section from meningeal surface of cerebral cortex. The lesion is similar to figure 1, but extends into the meninges. × 240.

rhage and edema were seen in other sections from the lungs. In the liver the Kupffer cells appeared prominent. Numerous round caseous foci without cellular detail were encountered. Necrotic areas of varying size were distributed in the splenic pulp but were more often observed in the lymph nodules. Macrophages with indistinct outlines could be seen in the periphery of some of these foci. An occasional necrotic focus extended into and some through the capsule. A thin sheet of exudate of fibrin, nuclear detritus and an occasional recognizable macrophage covered the spleen. Also there was diffuse hyperplasia of the reticulo-endothelium and the sinuses were congested.

Coagulation necrosis of minute aggregates of large mononuclear cells was noted

in the medulla and reticular zone of the suprarenal. The endometrium of the uterus was diffusely infiltrated with macrophages, some of which were collected in small groups which appeared necrobiotic (figure 3). Many macrophages were filled with engulfed particles of nuclear débris. In the distal end of the appendix the mucosa and the submucosa were infiltrated with many large mononuclear cells laden with nuclear débris. There was confluent focal necrosis of the mucosa with ulceration. An exudate of fibrin and macrophages was present on the serosa (figure 4). In the axillary, tracheo-bronchial and supra-pancreatic lymph nodes there was diffuse

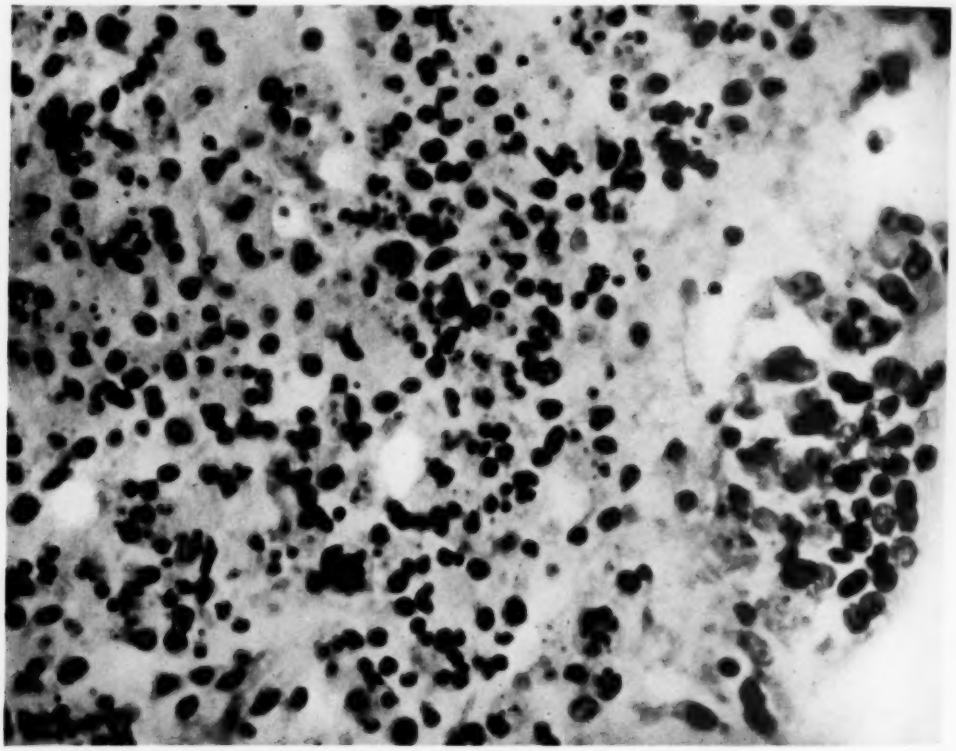

FIG. 3. Section from endometrium. Disorganization of the endometrium and infiltration with numerous macrophages, some engulfing nuclear detritus. There is a tendency to grouping of these cells. × 1000.

reticulo-endothelial hyperplasia and the sinuses were crowded with macrophages Necrotic foci without cellular detail were noted. The largest areas occurred in the axillary nodes.

No acid fast organisms could be found in sections from the brain, lymph nodes, lungs and spleen. Routine sections from the heart, aorta, thyroid, kidney, bladder, ovary and pancreas revealed no noteworthy changes. Blood serum, obtained at necropsy and examined by the laboratory of the Georgia State Board of Health, agglutinated *Bacterium tularense* in dilutions from 1:640 to 1:1280.

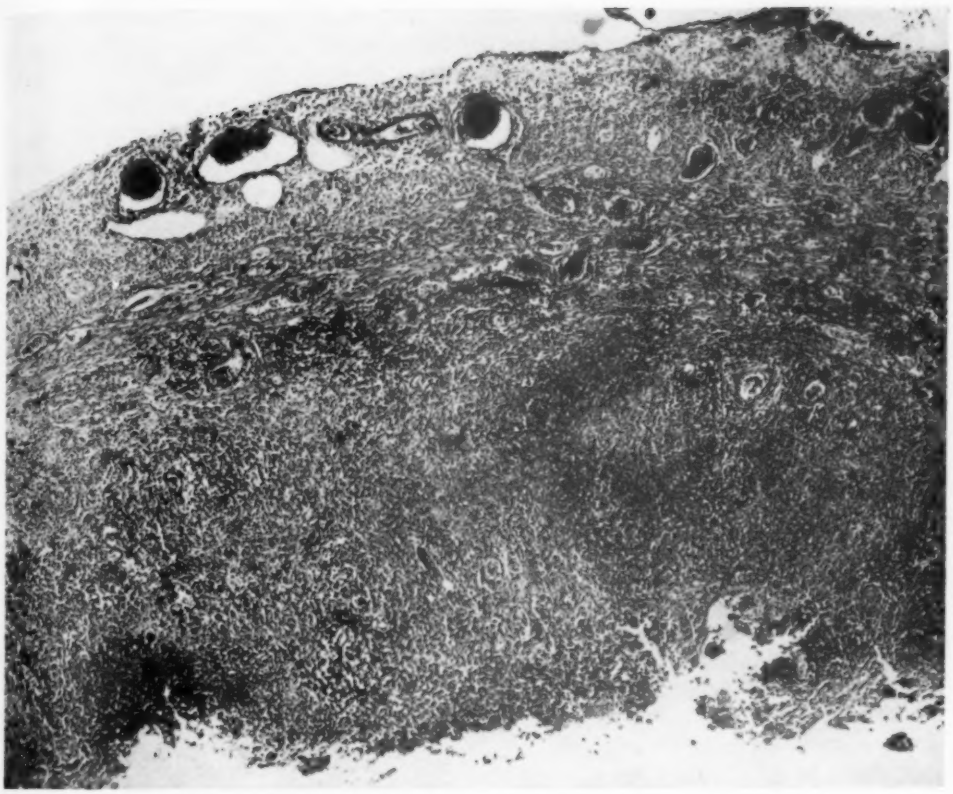

FIG. 4. Section from proximal third of appendix. Note the necrosis and ulceration of the mucosa. Dense infiltration with macrophages. × 75.

COMMENT

In this case the lesions of the central nervous system are of especial interest both from the clinical and pathologic standpoint. Meningeal symptoms have been noted not uncommonly in patients with tularemia, but the existence of tularemic meningitis was first demonstrated by Haizlip and O'Neil. In their fatal case with meningeal symptoms the brain and cord were not examined at necropsy, but injection of the spinal fluid produced tularemia in a guinea pig. In the literature we found only one description of the histopathology of tularemic meningitis, the case reported by Bryant and Hirsch. They described lesions in the meninges, submeningeal brain tissue, ependyma, subependymal tissues and choroid plexus. The involvement of the brain was considered an extension from the lesions of the meninges. Our observations differ from theirs in that isolated foci were seen within the confines of the brain (figure 1). The difference is probably due to the fact that our case represents an earlier stage in the pathology of the disease; their patient died on the sixteenth day of illness while ours died on the tenth day. It would seem from our observation that the meningitis occurred secondary to tularemic encephalitis. Lesions in the brain

without meningitis have been reported by Hartman. In a case of tularemia he found soft, grayish yellow, necrotic or hemorrhagic areas from 0.5 to 3 mm. in diameter in the corpus callosum, basal nuclei, pons and the adjacent tissue. Microscopically these lesions were characteristic of those produced by the *Bacterium tularense*. The manner of production of tularemic meningitis is probably the same as in tuberculous meningitis. Rich and McCordock have shown that tuberculous meningitis has its origin in the discharge of bacilli into the cerebro-spinal fluid from adjacent older caseous tuberculous foci. In the 24 necropsies previously reported, the brain and meninges were examined in only four cases. Two of these exhibited the lesions described above. The case of Foulger, Glazer and Foshay showed no noteworthy changes in the brain and meninges, while Palmer and Hansmann described a minute pontile hemorrhage and noted elevations on the pia-arachnoid due to several layers of fatty endothelial cells.

Our report is of further interest because lesions were observed in the appendix, thymus and uterus. In the reported 24 necropsies the inflammatory reaction of tularemia was observed in the spleen in 21, lungs in 20, lymph nodes in 20, liver in 19. Involvement of the other organs is rare. Our case exhibited microscopic foci of necrosis in the suprarenal. Francis and Callender have previously noted lesions here. Bardon and Berdez described congestion and swelling of Peyer's patches and solitary follicles of the intestine, and numerous small yellow patches were noted in the mucosa of the stomach and of the small and large intestine, but they did not describe these lesions microscopically. Simpson, and Bunker and Smith observed congestion of the mucosa of the stomach and intestines. Foulger, Glazer and Foshay described the lining of the entire gastrointestinal tract as dull, dirty, grayish pink with engorgement of the blood vessels. Microscopically they observed a diffuse and focal lesion on the serosal surface which was characteristic of tularemia. In Bernstein's first case scattered punctate hemorrhages were seen in the gastric mucosa; in the second, ulceration of the esophagus was noted; in the third, a necrotic focus occurred in the tonsil. Beck and Merkel described grossly and microscopically small ulcers of the stomach, duodenum, ileum and ascending colon which showed the typical necrosis and leukocytic infiltration. The cellular infiltration was confined to the mucosa. Theirs was a fatal case of the typhoid form caused by the ingestion of rabbit. In our case there was a distinctive tularemic appendicitis with local peritonitis which was recognized grossly and confirmed microscopically. No other lesions were seen in the gastrointestinal tract. Sections from the proximal two-thirds of the appendix revealed no lesions. Here then, we have a focal involvement of the appendix which could be hematogenic, yet the possibility of a primary intestinal lesion should be considered. As mentioned above, the only case that exhibited ulcers of the stomach and intestine was reported by Beck and Merkel and in this instance the infection was caused by ingestion of rabbit. It is not unreasonable to think that there may be two sites of inoculation, especially since the person who dresses the infected animal usually eats it. This would explain the fulminant course of some cases because of easy hematogenous dissemination from the intestinal tract. That it is not necessary for the ingested organisms to produce a gastrointestinal lesion is evidenced by the report of Amoss and Sprunt. In their case no gastrointestinal lesions were found although the disease was contracted by ingestion of rabbit. The ap-

pendicitis and serositis of the spleen explain the abdominal tenderness in these regions and the rigidity that developed later.

Involvement of the thymus and uterus has hitherto not been reported. While we observed no foci of necrosis in the thymus, there was hyperplasia of the reticulum, a change also noted in the liver, spleen and lymph nodes. The thymus was the only site where giant cell formation occurred. In the uterus of our case there was diffuse endometritis. Kavanaugh observed three patients who contracted tularemia during pregnancy and were delivered of normal babies during the height of infection. In one case labor was premature. Nor did coexisting tularemia endanger pregnancy in the patient of Bowe and Wakeman. A lesion of the uterus probably occurs rarely yet is one to be considered when pregnancy is complicated with tularemia.

Summary

A case of tularemic meningitis is described.

The meningitis is apparently secondary to hematogenic encephalitis.

The distribution of the lesions of the reported fatal cases of tularemia is summarized and involvement of the uterus, thymus and appendix is described.

The possibility of double infection, by way of the skin and gastrointestinal tract, is suggested.

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RENAL AMYLOIDOSIS WITH CLINICAL FINDINGS SUGGESTIVE OF POLYCYSTIC KIDNEY *

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SINCE the beginning of the aseptic era in surgery, general amyloidosis appears to be common only in sanatoria for the care of tuberculous patients. Dixon reported 100 cases of pulmonary tuberculosis, 70 of whom had amyloidosis. Perla and Gross reported 100 cases of amyloidosis out of 112 cases of pulmonary tuberculosis, and Saleeby 41 out of 50 cases. In a series of 579 autopsies at Glen Lake Sanatorium, 109 cases of amyloidosis were discovered, an incidence of 19 per cent. The incidence is less than is usually quoted by the various authors from other sanatoria. Rosenblatt found amyloidosis in 24.4 per cent of 451 necropsies and Perla and Gross in about 25 per cent of 400 post mortems.

Of our 109 cases of amyloidosis, the following was in every respect the most unusual:

CASE REPORT

At the age of 16 years, the patient had a cervical adenitis; at 18, cough, expectoration containing tubercle bacilli, high fever, and a pulmonary hemorrhage. Upon his admission to the Sanatorium in September 1921, shortly after the above symptoms were noted, fibroid pulmonary tuberculosis of the right middle and the left upper lobe was present as well as cavitation in the left upper lobe with a small spontaneous pneumothorax at the apex. The urine showed no abnormalities, and his blood pressure was 116 systolic and 60 diastolic. In 1922, a diagnosis of intestinal tuberculosis was made. Sufficient retrogression of both his pulmonary and intestinal lesions occurred so that on November 1, 1924, he was discharged with his tubercu-

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losis considered arrested. He remained in good health for three years and had, during this interval, many urinalyses which showed no abnormal findings.

In 1927, albumin was found in the urine in addition to hyaline, granular, and waxy casts. In February 1928, he developed an upper respiratory infection associated with pain in the right lumbar region. His blood pressure was 153 systolic and 105 diastolic. His urine contained 3 plus albumin and many casts; phenolsulphonephthalein excretion was 22.5 per cent, blood urea 38 mg., and non-protein nitrogen 77 mg. per cent. In January 1930, he was confined to bed for four days because of an acute upper respiratory infection; his right kidney was palpable and tender at this time. He had many recurrences of these respiratory infections and "kidney pains." In February 1932, the lymph nodes on the right side of his neck became palpable, enlarged, and eventually suppurated with the formation of a sinus which healed after four months.

Between 1930 and 1932 his blood pressure varied between 130 systolic and 88 diastolic and 148 systolic and 102 diastolic. In May 1932, it was 128 systolic and 80 diastolic. His urinalysis showed: specific gravity 1.017; albumin 3 plus; a few hyaline casts with fat droplets and very occasional granular casts. The hemoglobin was 87 per cent (11.98 gm.) and red blood cells 4,600,000.

Following an acute upper respiratory infection in February 1934, the blood pressure was 144, and the urine analysis showed the following: specific gravity 1.017, albumin 4 plus, a few hyaline and granular casts. Although the patient was known to have had a persistent and usually heavy albuminuria for about six years, and on several occasions a slight transient edema, he had no enlargement of his liver or spleen nor demonstrable active tuberculosis at this time. Because of the urinary findings, a diagnosis of amyloidosis was made.

An acute upper respiratory infection in October 1934 was followed by repeated vomiting for several days, so that fluids could not be retained. Urine showed: albumin 4 plus, erythrocytes, many leukocytes, and many casts; blood non-protein nitrogen 39 mg. and urea nitrogen 27.3 mg. per cent. Blood pressure 126 systolic and 90 diastolic. No edema was present. This episode marked the onset of the terminal phase of his illness. Upon advice, he resigned his position which he had held since 1925.

He was hospitalized on October 25, 1934. His blood pressure was 126 systolic and 90 diastolic. Urinalysis showed: Specific gravity 1.012; albumin trace; white blood cells 10–15; red cells 1–2 per high power field. Non-protein nitrogen was 39 mg., blood urea nitrogen 27 mg. per cent. There was a gradual drop in urinary output, and on November 1 and 2, his output was only 100 c.c. and 80 c.c. respectively. On the day of the low output his blood urea nitrogen was only 18.5 mg. and creatinine 1.9 mg. per cent. For the previous three days his intake was never below 2000 c.c. and on November 1 reached a maximum of 2950 c.c. On November 2, the patient was drowsy, and his speech was retarded. On November 3, he was given two intravenous injections of 25 per cent dextrose in normal saline, 300 c.c. each, and on that day his output increased to 325 c.c. The Karell treatment was instituted on the same day with 210 c.c. of skimmed milk every six hours. November 4, the 24 hour output reached 580 c.c. On November 6, the Karell treatment was discontinued, and the patient was allowed 1000 c.c. of fluids. After this time, urinary suppression caused no further concern so that by November 9, his output was 1250 c.c. and for the first time exceeded his intake (figure 1). During the period of urinary suppression and forced fluids, there was no edema and the feces were large, soft, and not increased in number.

About November 1, there was a distinctly palpable mass in the right upper quadrant of the abdomen. This was considered to be the right kidney by most observers, although a surgical consultant considered that an upper abdominal malignant growth, particularly carcinoma of the proximal portion of the transverse

colon, should be considered. This mass remained palpable for about one month. A cystoscopic examination showed a pelvic deformity of both kidneys which very strongly suggested polycystic disease (figure 2). Because of the roentgen findings simulating polycystic disease of the kidneys and because one kidney was palpable, the diagnosis of renal amyloidosis or chronic glomerulo-nephritis, with nephrotic component, was changed to polycystic disease of the kidneys.

On November 27, the patient developed an acute, non-contagious parotitis on the right side. This was accompanied by fever, elevation of pulse rate, and toxemia.

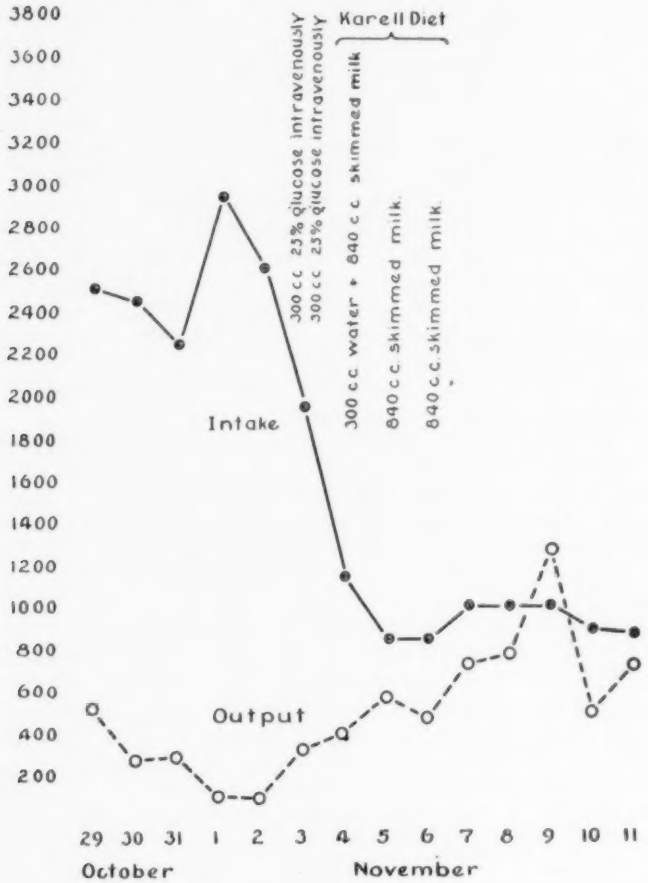

FIG. 1. Chart of the patient's intake and output showing the change after the Karell diet.

Four days prior, the first evidence of edema in the ankles was noted, but diminished on a salt free diet. On December 7, the parotid swelling had greatly diminished and soon disappeared. The blood pressure was 150 systolic and 96 diastolic. The right kidney, which could be felt as low as the umbilicus a month previously, had greatly diminished in size.

On November 18, an intravenous phenolsulphonephthalein showed no dye excretion within two hours. This was repeated on November 26 with the same result. On November 28, the blood urea nitrogen was 49.6 mg. and the creatinine 3.0 mg. per cent.

On January 3, 1935, the hemoglobin was 50 per cent, Sahli, in contrast to 75 per cent on entry. The blood urea nitrogen was 50.7 mg. per cent. The patient was put on 0.5 gram of reduced iron three times a day. On February 16, the hemoglobin had increased to 72 per cent and one month later, with the patient near death, it was 62 per cent although iron had been discontinued for two weeks.

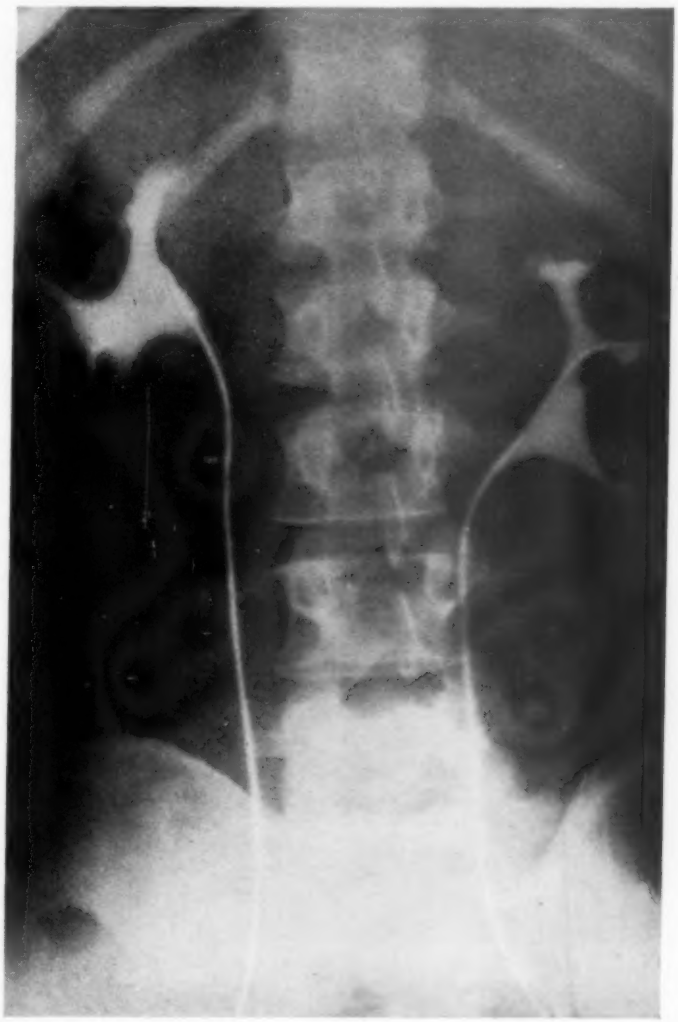

FIG. 2. Retrograde pyelogram showing the widened and elongated renal pelves and calices suggesting polycystic disease of the kidneys.

Edema became a troublesome and an increasing feature of the patient's illness after February 14. On March 5, stool specimens contained large amounts of red blood. On March 13, the blood pressure was 180 systolic and 110 diastolic. Urinalysis showed: Specific gravity 1.009; albumin trace; white blood cells 8–10 per high power field. On March 24, he began to vomit bright red blood and continued to do so for several days. His edema became more marked, and there was a gradual rise

of the blood urea nitrogen (highest 59.3 mg. per cent). Marked fatigue, vomiting, and signs of uremia increased until April 15, 1935 when death occurred.

Autopsy Report. Postmortem examination revealed a marked generalized edema, a non-tuberculous fibrinous pericarditis, and a decubital ulcer over the sacrum.

The lungs contained numerous irregularly scattered, healed, calcified nodules varying in size from 2 to 6 mm. The apices were puckered and fibrotic. Three thin

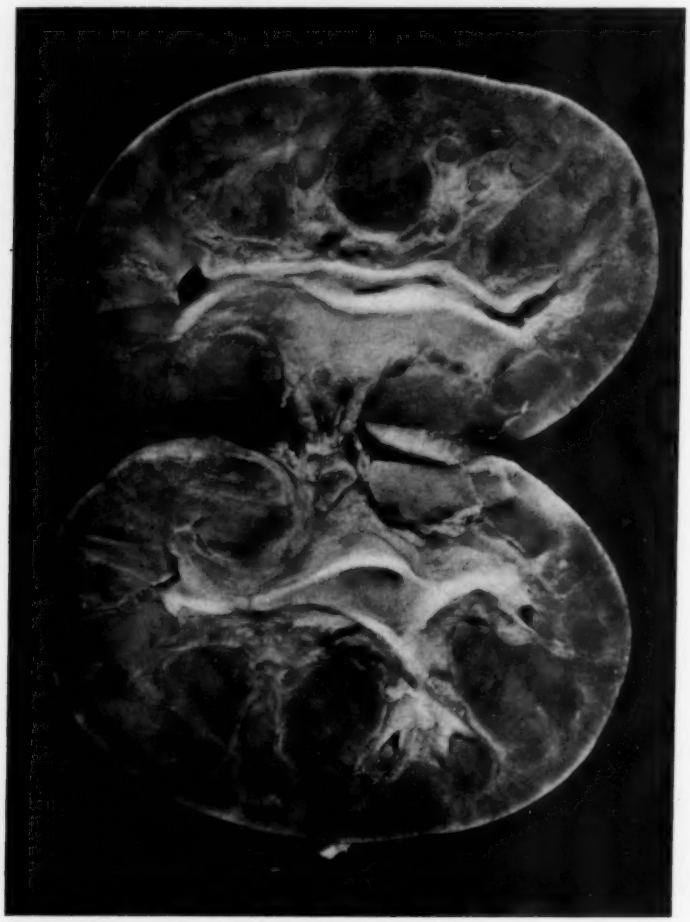

FIG. 3. Photograph of the right kidney showing the enlarged pelvis and the narrowing of the renal cortex. The shape of kidney pelvis and the narrowing of the renal cortex are evident.

walled cavities, each 7 mm. in diameter, were situated in the left apex; these were filled with thick white pus in which no organisms were found.

The spleen weighed 112 grams, the liver 1500 grams. They showed no evidence of disease. The right kidney was situated 8 cm. lower than the left and the ureter was correspondingly shorter. The right kidney weighed 85 grams, the left 95 grams. The parenchyma was firm, waxy, and the distinction between the cortex and medulla had almost disappeared. The pelves, although not distended, appeared larger than normal and extended nearer the poles of the kidneys than is usual. (Figure 3.)

Microscopic examination: In the left lung there are several minute calcified nodules surrounded by giant and epithelioid cells and lymphocytes. The cavity walls show a similar activity.

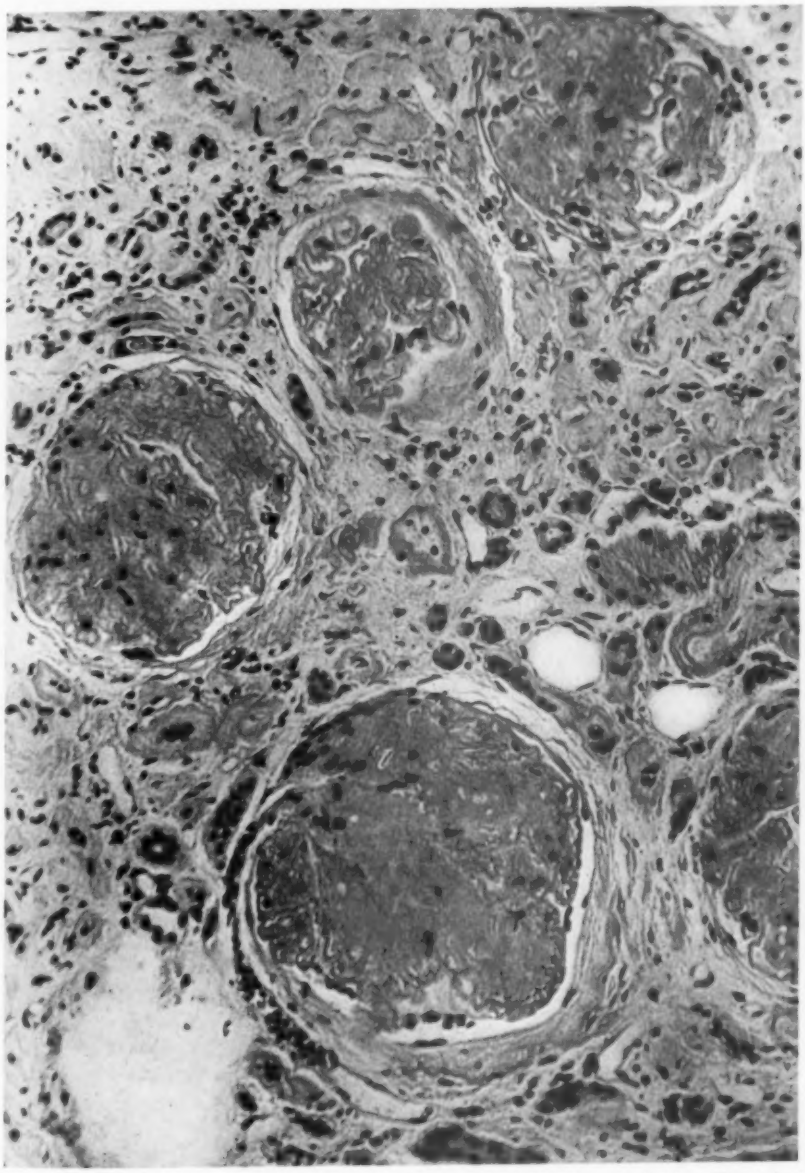

FIG. 4. Microphotograph. The glomeruli are almost occluded by amyloid. The tubules are atrophic and frequently have marked deposits of amyloid.

The pericardium appears acutely inflamed. There is a fibrinous exudate on the surface, and the membranes are infiltrated with polymorphonuclear neutrophiles.

The small blood vessels of the liver and spleen appear slightly thickened. The

media contains a slight amount of amyloid. The hepatic parenchyma is slightly fatty but otherwise shows no evidence of disease. The malpighian corpuscles of the spleen occasionally contain a slight deposit of amyloid.

The renal glomeruli are occasionally normal in size, but usually they are small and contracted. Each glomerulus appears to be filled with amyloid. Few capillaries containing blood are demonstrable. The remnants of the tubules appear as thin tubes of amyloid with casts and some desquamated epithelium in the lumina. (Figure 4.)

Discussion

This case represents one in which the amyloid disease is almost wholly confined to the kidneys. It is unusual, for that reason, and also for the fact that it did not have the usual provocative causes so often associated with amyloid disease. It is true that the patient had pulmonary tuberculosis and was confined to the Sanatorium for two and one-half years (1921–1924). Yet, from 1924 until the time of his death, he was examined from two to four times a year, both by physical and roentgen examination, and there was no evidence of activation of his pulmonary tuberculosis. The first sign of amyloid disease appeared during this period of inactivity of his tuberculosis (1927). He did have suppuration of the right cervical glands two years prior to death. This lasted only four months and was considered tuberculous even though this could not be proved either by direct smear or guinea pig inoculation. But since this suppuration did not appear until five years after his first urinary findings, it cannot therefore be considered a predisposing factor.

The limitation of the amyloidosis to the kidneys is quite uncommon. In Bell's series of 65 cases, only two had the amyloid confined to these organs. Raubitschek found only two cases in a series of 72, in which the liver and spleen were not involved. In our own series of 109 cases, the kidneys were the almost exclusive sites of deposit in only this one instance. Since the publication of Bell's paper in 1933, amyloidosis involving the kidneys alone has been reported by Rosenblatt (2) and Perla and Gross (2).

In every instance in Bell's series of 33 cases with tuberculosis, there was extensive chronic suppuration. In our case the suppuration was present in the form of minute cavities, but these were so small that it seems unlikely they would cause the changes which led to death. They could not be seen on roentgen examination. The pulmonary tuberculosis was certainly inactive until the terminal stages. The cavities gave no symptoms whatever, and each of the three cavities was only 7 mm. in diameter.

Death from amyloid disease by uremia, although quite rare, is probably more common than is generally supposed. Perla and Gross go so far as to state that "Uremia complicating amyloidosis of the kidney has been observed not infrequently. . . ." Bell found only 10 cases reported before 1933, and since that time there are only nine reported by the following: Dixon (1), Perla and Gross (2), Carey (1), Willer (2), Fahr (1), Langeron et al. (1), and Mahoudeau et al. (1).

The roentgen picture of the kidney is unique. We have been unable to find another case in which the pelves were so deformed as to give the appearance of large kidneys. Moreover, the presence of large and a somewhat irregular mass detectable on casual palpation seemed to lend confirmation to the diagnosis of polycystic kidney. The presence of a mass in the right upper quad-

rant can be accounted for by the low position of the right kidney, but the apparent decrease in size still lacks a satisfactory explanation.

Summary

1. At the time of onset of the renal amyloidosis, the patient had arrested pulmonary tuberculosis with no extra-pulmonary complications. His early history, however, revealed two conditions found in association with amyloid, namely, adenitis and enteritis.

2. The patient's intake and output over a period of observation, illustrates a paradoxical diuretic response to the forcing and probably to the limitation of fluid intake, and the diuretic effect of concentrated dextrose given by vein and skimmed milk administered according to Karell procedure in urinary suppression.

3. The presence of a mass in the right upper quadrant and the roentgen findings of the renal pelves led to an erroneous diagnosis of bilateral polycystic kidney.

4. The patient died in uremia due to renal amyloidosis.

5. Unusual also was the recovery from non-contagious parotitis and the unexpected response to the administration of iron in the marked anemia accompanying renal insufficiency.

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EDITORIAL

VIRUS TUMORS

The volume and the highly specialized character of investigative work on the nature of malignant growths has to some extent rendered this field of medicine an obscure one for physicians. Certain recent advances in our knowledge of tumor producing agents may well have escaped general recognition.

In the early years of this century the possibility of the transmission of certain spontaneous new growths of animals to others of the same species by inoculation of bits of tumor tissue gained acceptance. Jensen in 1902 through his careful studies of the transmission of a spontaneous carcinoma of a white mouse helped greatly clearly to define the conditions necessary for the success of such inoculations. In the course of his investigations, he studied the behavior of the fragment of implanted growth. It was his purpose to determine whether the tumor that resulted arose from the tumor cells that had been injected, or from the cells of the host's tissues. By histological study of different stages, he concluded that whereas the central portion of the implant underwent necrosis, the marginal cells multiplied and formed the new growth. This indicated that these tumors were in a sense tissue cultures *in vivo* and that by repeating transfers, one was carrying on indefinitely the same race of cells. This conclusion of Jensen's accorded well with the studies of the period which had failed to disclose in neoplasms any extracellular infective agent which could be considered causative. It seemed to place the tumor cell itself in the position of being the ultimate carrier of the disease. The search for bacteria, fungi, or protozoa which could cause cancer remained fruitless, and infection as a cause for neoplasms appeared less and less likely.

The nature of irritants which acted as a factor in stimulating neoplastic growth came to be the central problem of cancer research on etiology and, especially since the discovery of coal tar cancer in animals by Yamagiwa and Itchikawa in 1915, this subject of chemical carcinogenic agents has been most intensively investigated.

In 1911, however, the theory of infection as a cause for neoplasms was rejuvenated by the publication of Peyton Rous' discovery of a chicken tumor which could be transmitted by a cell free filtrate of the tumor tissue. The widespread confirmation of this work and its further extension to certain other tumors of fowls proved conclusively that, in the case of these neoplasms at least, some other agent than the living tumor cell could transmit the neoplasm to closely related animals of the same species. Moreover, the growths incited in the host's tissues by the injection of the tumor filtrate were sufficiently similar to indicate a tissue specificity of the tumor-producing effect.

The nature of the agent in the tumor filtrate is still unknown in spite of intensive study of the problem. Many of its attributes, however, have been determined. It is invisible; it is filtrable; it is about 100 Mμ in size; it is dependent for increase upon association with living cells; it induces the formation of neutralizing antibodies which act upon it *in vitro* but from which it is protected *in vivo* by its association with cells; it causes morbid changes in cells and induces proliferation to cause neoplasms. The growth of knowledge concerning virus diseases has shown that such are the attributes of certain types of viruses. As Rous has recently succinctly stated: A comparison " makes plain that the agents must be termed viruses or else that the criteria must be rejected whereby the latter are now recognized as such."

The classification of the agent as a virus does not of course settle the matter as to whether it is to be considered as living matter or an inanimate stimulus. This fundamental question is still an open one for all the viruses.

More vital is it to know how large a part viruses, whatever their ultimate nature, may play in the genesis of tumors. For many years their importance seemed relatively circumscribed, since no virus tumor of mammals had been observed. However, recently a virus-induced papilloma of wild rabbits has been described by Shope and intensively studied by Rous and others. A filtrate of this tumor was found to cause abundant warty growth when rubbed on the abraded skin of the domestic rabbit. In this animal the growth did not always retain the characteristics of a benign papilloma but instead developed typical cancerous growths with not infrequent metastases to regional glands and to the lungs. The virus can not be demonstrated in extracts of these cancers. The question therefore arises whether the cancerous transformation is due to the virus or to some further cause acting upon the virus induced papilloma. Rous notes, however, that in certain instances he has transferred cancer tissue from a metastasis of the original growth to the tissues of another rabbit and that with the growth of this implant this second animal developed in its blood neutralizing antibodies for the original virus. This speaks at least for the continued presence of the virus in the malignant stage of the growth.

The production of cancerous growths in a mammal by means of a virus will stimulate even greater interest in this type of carcinogenesis. The determination of the ultimate significance of viruses in the etiology of cancer must await, however, the results of many future investigations.

REVIEWS

Eugenical Sterilization. By The Committee of the American Neurological Association for the Investigation of Eugenical Sterilization. 211 pages; 22 × 15 cm. The Macmillan Company, New York City. 1936. Price, $3.00.

This book is the published report of a special committee of the American Neurological Society. The report first presents a brief history of legal sterilization and then a summary of the existing laws in the United States and in foreign countries. A critical review follows of the main arguments for sterilization; the reputed increase of insanity and defective mentality; the reputed increased propagation rate of the mentally diseased or defective; and the inheritability of mental diseases. The available data are shown to render questionable the validity of these assumptions unless in greatly qualified form. The Committee felt it could only recommend sterilization in selected cases of certain diseases and then only with the consent of the patient or those responsible for him. This book is a valuable corrective to much loose thinking and writing on this subject.

M. C. P.

Failure of the Circulation. By TINSLEY RANDOLPH HARRISON, M.D. 396 pages; 23 × 15½ cm. The Williams & Wilkins Company, Baltimore, Maryland. 1935. Price, $4.50.

Students of the pathologic physiology of the circulation have followed with interest the investigations of Dr. Harrison and his colleagues at Vanderbilt University. In this volume a point of view attained by this group as to the meaning and mechanism of congestive heart failure is ably presented. No attempt is made to minimize the uncertainty still prevailing as to the nature of certain phenomena, but from the existing data a strong argument is drawn that backward failure, or back pressure from the left and the right ventricles is the source of the congestive process. Diminished cardiac output is shown to be often present in conditions unaccompanied by evidence of congestive failure and to be often absent in typical instances of congestive failure. Hence it is argued "forward failure," or diminished output, cannot explain congestive failure. The discussion of the significance of cardiac dilatation and hypertrophy is of particular interest.

The sections dealing with failure of the "shock" type and failure through coronary disease seem much less adequate than the main section of the book. The inclusion under coronary disease of purely clinical description and of therapeutic recommendations does not seem in keeping with the purpose of the volume.

The frank espousal of a theory is much more stimulating than the mere presentation of a mass of data. The book should interest every thoughtful clinician.

M. C. P.

An Index of Treatment. By various writers; edited by ROBERT HUTCHINSON, M.D., LL.D., F.R.C.P. Eleventh Edition, Revised. Super Roy. 8 vo. 1020 pages; 18 × 26 cm. Wm. Wood and Co., Baltimore. 1936. Price, $12.00.

This work is a companion volume accompanying texts on Symptomatology, Diagnosis, and Prognosis. It attempts to cover within the space of a thousand pages the therapy of practically every medical and surgical condition on record. Obviously such discussion must be brief.

To the reviewer it seems neither wise nor practical to present the operative therapy of acute appendicitis, together with the management of its complications

and after-treatment, within the space of two pages. In the hands of one in need of such information, it might be more dangerous than helpful. The same comment might be offered concerning many of the operative procedures described—none of which should be attempted without a background of surgical experience which would render such discussion unnecessary.

While the medical topics discussed are not subject to the above criticisms, they are of necessity brief. Many methods are mentioned which may rightly be considered outmoded—the use of leeches, for example, as recommended for relief of pleuritic pain in pneumonia, and precordial pain in acute rheumatic carditis. The section on poisons might be of convenience for ready reference. The discussion of hypnotism would seem of little value to the average reader of the volume. The method of antiluetic therapy advised is not adequate according to the standards established in this country, and adherence to it might give rise to dangerous end-results.

In our opinion this volume cannot be said to fulfill satisfactorily the implications of its title.

G. W. B.

COLLEGE NEWS NOTES

Nominations, 1937–38

Elective Offices

Dr. James H. Means, President-Elect, Boston, Mass., accedes to the Presidency.

New Nominations

President-Elect ..... William J. Kerr, San Francisco, Calif.
First Vice-President ..... David P. Barr, St. Louis, Mo.
Second Vice-President ..... G. Gill Richards, Salt Lake City, Utah
Third Vice-President ..... William Gerry Morgan, Washington, D. C.

Respectfully submitted,

Committee on Nominations,
William B. Breed
James D. Bruce
Charles T. Stone
Charles F. Martin
George Morris Piersol, *Chairman*

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts by the authors to the College Library of publications by members:

Books

Dr. Howard T. Karsner (Fellow), Cleveland, Ohio—one autographed book, "Human Pathology," Fourth Edition;
Dr. W. McKim Marriott (Fellow—Deceased), San Francisco—one book, "Infant Nutrition";
Dr. F. M. Pottenger (Fellow), Monrovia, Calif.—one autographed book, "Tuberculosis in the Child and the Adult";
Dr. Paul D. White (Fellow), Boston, Mass.—One autographed book, "Heart Disease," Second Edition;
Dr. Clarence J. Tidmarsh (Associate), Montreal, Que.—one book, "Chronic Indigestion."

Reprints

Dr. William E. Ash (Fellow), Council Bluffs, Iowa—1 reprint;
Dr. John L. Goforth (Fellow), Dallas, Tex.—1 reprint;
Dr. William A. Groat (Fellow), Syracuse, N. Y.—1 reprint;
Dr. Manfred Kraemer (Fellow), Newark N. J.—1 reprint;
Dr. D. O. N. Lindberg (Fellow), Decatur, Ill.—1 reprint;
Dr. Harry R. Litchfield, Brooklyn, N. Y.—1 reprint;
Dr. Fred M. Meixner (Fellow), Peoria, Ill.—1 reprint;
Dr. George R. Minot (Fellow), Boston, Mass.—2 reprints;
Dr. Edgar A. Hines, Jr. (Associate), Rochester, Minn.—4 reprints;
Dr. Maurice S. Jacobs (Associate), Philadelphia, Pa.—5 reprints;
Dr. Leslie M. Smith (Associate), El Paso, Texas—3 reprints.

We also gratefully acknowledge the gift of the following books to the College Library by the author, Dr. Charles Solomon, Brooklyn: "Pharmacology, Materia Medica and Therapeutics"; "Prescription Writing and Formulary."

New Life Members

The following have become Life Members of the American College of Physicians at the dates indicated, making a total of seventy-seven Life Members:

Dr. Samuel A. Vogel, Buffalo, N. Y., January 25, 1937;
Dr. Mills Sturtevant, New York, N. Y., February 4, 1937;
Dr. Russell M. Wilder, Rochester, Minn., February 5, 1937.

Annual Meeting of the Nebraska Members of the College

The Nebraska College Meeting was held January 13, Lincoln, Nebraska, Hotel Cornhusker.

A scientific program was held during the afternoon, which was followed by a banquet at 6:00 p.m. A short business session followed the dinner and then the scientific program was continued. It was a very enthusiastic meeting and it was decided that the next meeting would be held in Omaha.

Afternoon Program: Dr. J. C. Thompson (Fellow), "Desiccated Duodenal Mucosa in the Treatment of Anemia"; Dr. J. Marshall Neely (Fellow), "The Pathogenesis of Tuberculous Meningitis"; Dr. H. E. Flansburg (Fellow), "Report of an Atypical Case of Pulmonary Congestion Due to Congestive Failure"; Dr. H. J. Lehnhoff, "Report on Cases of Simon's Disease"; Dr. F. L. Rogers (Fellow) and Dr. G. W. Covey (Fellow), "Report of a Case of Thymoma with Cardiac Metastasis"; Dr. Edward Meister, "Report of Case of Coarctation of the Aorta." Dr. E. H. Hashinger (Associate), Kansas City, Mo., was the guest speaker of the evening and discussed "The Practical Side of Endocrine Therapy."

Adolph Sachs, M.D., F.A.C.P.,
Governor for Nebraska.

Meeting of the American Board of Internal Medicine

The Chairman of the American Board of Internal Medicine, Dr. Walter L. Bierring, has reported a meeting of the Board at Chicago, February 13, 14 and 15, 1937. A report on the candidates who took the Board's written examination, December 14, 1936, reveals that forty-eight candidates were passed and eight were recommended to repeat the examination in October, 1937. The next written examination is scheduled for March 22, 1937. The first practical or clinical examination will be conducted on Friday, April 23, at the City Hospital, St. Louis, Mo., beginning at 9:00 a.m., this being the closing day of the Twenty-First Annual Session of the American College of Physicians at St. Louis. The second practical examination will be conducted by members of the Board on Saturday, June 5, 1937, in Philadelphia.

Annual Congress on Medical Education and Licensure

The Thirty-Third Annual Congress on Medical Education and Licensure was held in Chicago, February 15 to 16, 1937. Among Fellows of the College who participated are the following:

Dr. William D. Cutter, Chicago, Ill., "Report of the Survey to Individual Schools";
Dr. R. L. Sensenich, South Bend, Ind., "The Doctor and the Narcotic Violator";

Dr. Torald Sollmann, Cleveland, Ohio, "The Why, What and How of the Medical Scholastic Aptitude Test";
Dr. Howard T. Karsner, Cleveland, Ohio, "Philosophical Comments on Examinations";
Dr. Harold Rypins, Albany, N. Y., "Increase in the Number of Practitioners in the Country";
Dr. Joseph C. Doane, Philadelphia, Pa., "How Nursing May Promote Inter-Professional Relationships."

Dr. F. H. Voss (Fellow), Kingston, N. Y., has been elected President of the Ulster County Medical Society for 1937. Dr. Voss also has been appointed by the Mayor as a member of the Board of Managers of the Kingston City Laboratory for a period of three years.

Dr. William C. Voorsanger (Fellow), San Francisco, delivered the third Lane Popular Medical Lecture February 5, 1937, under the auspices of the Stanford University School of Medicine, his subject being "Recent Advances in the Treatment of Tuberculosis."

Dr. L. D. Sargent (Fellow), Washington, Pa., has been elected a Trustee of the Pennsylvania State Medical Society and Councilor of the Eleventh District.

Dr. Fred M. Meixner (Fellow), Peoria, Ill., has been reëlected President of the Peoria County Tuberculosis Association. Dr. Meixner is a Director of the Illinois State Tuberculosis Association and also a member of a special committee, of which Dr. Maxim Pollock (Fellow), Peoria, is chairman, to plan a tuberculosis survey in the schools of the City of Peoria.

Dr. John C. Ruddock (Fellow) and Dr. Howard F. West (Fellow), both of Los Angeles, have been made President and Secretary-Treasurer, respectively, of the newly organized California Heart Association.

The First New Orleans Graduate Medical Assembly was held March 8–11, with a program of clinical demonstrations, didactic lectures, round table discussions and symposia. Among Fellows of the College outside of New Orleans who contributed to the program were: Dr. Anthony Bassler, New York City; Dr. Russell Cecil, New York City; Dr. John A. Kolmer, Philadelphia; Dr. Julius H. Hess, Chicago; and Dr. George Morris Piersol, Philadelphia.

Dr. Louis P. Hamburger (Fellow), Associate in Medicine, Johns Hopkins University School of Medicine, has been appointed consultant to the Baltimore City Health Department.

Dr. Thomas Hodge McGavack (Associate), formerly of San Francisco, has been appointed Associate Professor of Medicine at the New York Medical College and Flower Hospital.

Dr. J. Arthur Myers (Fellow), Minneapolis, addressed the forty-fifth annual meeting of the Pennsylvania Tuberculosis Society in Philadelphia on January 20.

Dr. J. Burns Amberson, Jr. (Fellow), has been promoted to Professor of Clinical Medicine on the Faculty of New York University College of Medicine.

Dr. Elmer L. Sevringhaus (Fellow), Madison, Wis., and Dr. Francis E. Senear (Fellow), Chicago, were among those who appeared on the program of the ninth spring clinical conference of the Dallas Southern Clinical Society, March 15 to 18.

A Pneumonia Commission has been appointed by the President of the Medical Society of Virginia, Dr. J. Morrison Hutcheson (Fellow), Richmond, to investigate the incidence and types of the disease in Virginia and the kind of management in vogue. Members of the Commission include Dr. Wyndham B. Blanton (Fellow), Richmond, chairman; Dr. Walter B. Martin (Fellow), Norfolk; Dr. Henry B. Mulholland (Fellow), Charlottesville; Dr. Philip S. Smith (Fellow), Abingdon; and Dr. Harry Walker (Associate), Richmond.

Dr. Milton M. Portis (Fellow), Chicago, is a member of the professional committee for medicine in the Illinois State Department of Registration and Education.

Dr. James H. Means (Fellow and President-Elect), Boston, addressed the North Side Branch of the Chicago Medical Society, February 4, on "The Rôle of the Physician in the Management of the Patient with Thyrotoxicosis."

Honorary fellowship in the Royal College of Physicians and Surgeons (Canada) was recently conferred upon Dr. Henry A. Christian (Fellow), Boston, Mass.

Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., Dr. Andrew C. Ivy (Fellow), Chicago, and Dr. Jonathan C. Meakins (Fellow), Montreal, were among the guest speakers at the fifty-third annual meeting of the Mid-South Post Graduate Medical Assembly, held at Memphis, Tenn., February 16 to 19.

Dr. Carl J. Wiggers (Fellow), Professor of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio, is on sabbatical leave, while on a trip around the world.

The Medical Society of the State of Pennsylvania has established a commission for the study of pneumonia control. Among the members of the commission are Drs. Edward L. Bortz (Fellow), Philadelphia, chairman; Edward W. Bixby (Associate), Wilkes-Barre; George J. Kastlin (Fellow) and Clifford C. Hartman (Fellow), Pittsburgh; T. Grier Miller (Fellow), Henry K. Mohler (Fellow) and Leon H. Collins, Jr. (Associate), Philadelphia.

Dr. Thomas Klein (Fellow) has been appointed Professor of Clinical Medicine at Temple University School of Medicine, Philadelphia.

Dr. Samuel B. Hadden (Fellow) has been promoted to Clinical Professor of Neurology at Temple University School of Medicine, Philadelphia.

Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service, was one of the principal speakers at the laying of the cornerstone of the U. S. Narcotic Farm at Fort Worth, Texas, February 13. This is the second narcotic farm to be built by the U. S. Public Health Service under the jurisdiction of the division of mental hygiene. The first was opened during May, 1935, at Lexington, Ky., where 1,240 patients were admitted during the first year of operation. The annual report of the Public Health Service states: "There is no question that the treatment of narcotic addiction in a hospital has distinct advantages over the management of such cases in a correctional institution."

Dr. Fred E. Clow (Fellow), Wolfeboro, N. H., was elected Secretary-Treasurer of the State Board of Registration in Medicine.

Dr. Josiah N. Hall (Fellow), Emeritus Professor of Medicine, University of Colorado School of Medicine, Denver, and a former Governor of the College for Colorado, was the guest of honor at a testimonial dinner, February 20, given by Dr. Hubert Work (Fellow), formerly Secretary of the Interior. Dr. Hall has retired from active practice as of March 1. He is seventy-seven years of age, a native of Chelsea, Mass., and a graduate of Harvard University Medical School, 1882. His medical career has been rich in experience and service. He has contributed much, has sown well; his harvest is one of many honors, of love and of appreciation. Tribute was paid him in 1936 by the Colorado State Medical Society when the banquet and president's reception were dedicated to him in recognition of his fiftieth year of attendance at the annual sessions of that Society.

Dr. George W. McCoy (Fellow), who since 1915 has been director of the National Institute of Health, formerly known as the "Hygienic Laboratory," has been relieved of this appointment to make investigations on leprosy. Dr. McCoy is a native of Cumberland Valley, Pa., is sixty years of age and a graduate of the University of Pennsylvania School of Medicine, 1898. He entered the Public Health and Marine Hospital Service in 1905 as assistant surgeon; in 1913 he became surgeon in the U. S. Public Health Service. He was named medical director July 1, 1930. From 1908 to 1911 he was in charge of the U. S. Plague Laboratory, San Francisco, and from 1911 to 1915 director of the U. S. Leprosy Station, concurrently serving during this period as sanitary adviser to the Hawaiian Government. He has written numerous papers on public health and bacteriological subjects. He was President of the Washington Academy of Sciences during 1935.

Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service, Washington, received the honorary degree of Doctor of Pharmacy at the 116th annual celebration of Founders' Day at the Philadelphia College of Pharmacy and Science on February 23. Dr. Parran delivered an address, "The Aims and Ideals of the United States Public Health Service."

ERRATUM

In the College News Notes of the January 1937 issue, page 1071, of the Annals of Internal Medicine, announcement was made that Dr. Elliott P. Joslin of Boston is President of the Interstate Post-Graduate Medical Association. Dr. Joslin is President-Elect at the present time; Dr. John F. Erdmann of New York City is President.

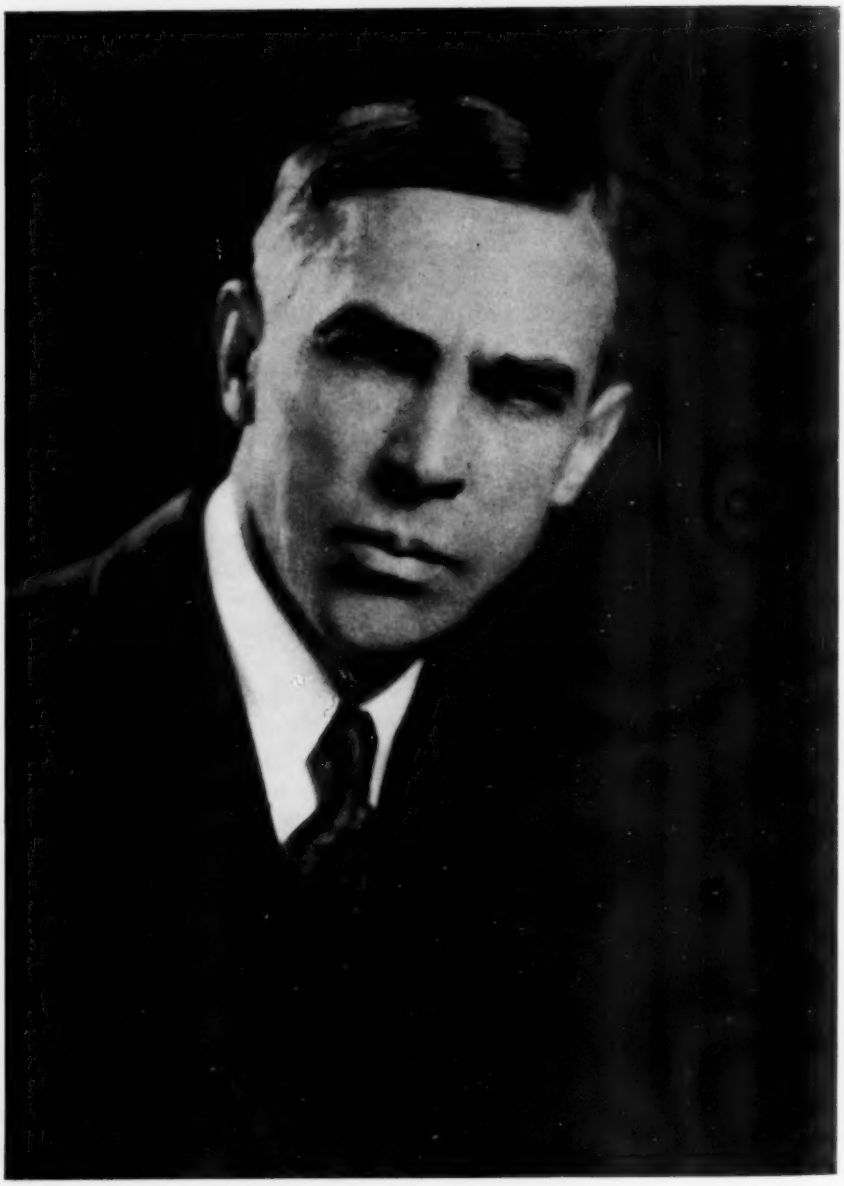
OBITUARIES

DR. LUTHER FISKE WARREN

Dr. Luther Fiske Warren was born in Waterford, Michigan, September 20, 1885, the son of Charles B. Warren and Anna Weinmann. He died on January 18, 1937, at his home, 81 Pierrepont Street, Brooklyn, after a long period of intense suffering, of generalized metastases resulting from a mammary gland carcinoma removed several years previously. He is survived by his widow, his mother, his two sons, Dr. Charles Ford and Dr. Robert Fiske, both connected with the Long Island College Hospital, a daughter, Miss Edith Warren, and a brother and sister.

From earliest childhood Dr. Warren began to exhibit his enormous capacity for work. As a small child he worked on the farm, while attending the local school. Going to Ann Arbor in order to complete the last two years of high school there, he began to shift for himself, working his way successively through the literary and medical schools of the University of Michigan. As a Freshman in the literary school he married Miss Agnes Chubb, a student in the dental school, and before he had finished his medical course his wife had borne him two children, and had had an operation for gall-stones. In spite of the cares connected with providing for this family, in his junior year in medical school he was elected to the honorary fraternity, Alpha Omega Alpha, and in his senior year to Sigma Xi. He received the degree of A.B. in 1907 and M.D in 1909. Following his graduation from medical school he was kept on as Instructor in Medicine, teaching physical diagnosis and giving the first course in clinical microscopy ever given at the School. As a result, even though so young, he was frequently called in consultation by older physicians in Ann Arbor. During the three years of this work his daughter was born.

In 1912 Dr. Warren was called to the Long Island College Hospital, Brooklyn, to be director of the newly established clinical laboratories, with the title of Assistant Professor of Clinical Medicine. His prodigious energy and remarkable teaching ability resulted in rapid promotion. From 1915 to 1917 he was Associate Professor of Medicine; from 1917–1919, Acting Professor of Medicine, and in 1919 was made Professor of Medicine. With the reorganization of the College in 1930, he became Professor of Medicine of the Long Island College of Medicine, a post he was holding at his death. He also held many other medical appointments in Brooklyn, being Physician-in-Chief at the Long Island College Hospital and St. Johns Hospital, Medical Director of the Brooklyn Home for Consumptives, which he completely reorganized after his appointment in 1931, and Consulting Physician to the Methodist Episcopal, Coney Island, Harbor, Lutheran, Southside and Brunswick General Hospitals.



DR. LUTHER F. WARREN

REGENT OF THE AMERICAN COLLEGE OF PHYSICIANS

Dr. Warren's medical society memberships were very extensive and he held many official positions in them. A Fellow of the American College of Physicians since 1919, he was Governor from 1931 to 1933 and a Regent from 1933 until his death. He served on many committees, giving most of his time and service to the Committee on Credentials. He was an advisor to the American Board of Internal Medicine. Memberships in national societies included the American Medical Association, American Heart Association, National Tuberculosis Association, Association for Study of Internal Secretions, American Society of Tropical Medicine, American Society for the Advancement of Science. Local societies included the New York Academy of Medicine, Medical Society of the County of Kings (President, 1930), Brooklyn Society of Internal Medicine, Brooklyn Pathological Society, Brooklyn Medical Association and Associated Physicians of Long Island. He was Chairman of the Public Relations Committee of the Medical Society of the State of New York. In addition to the enormous amount of time spent in teaching, in administration of his departments in the medical school and hospital and in his medical society activities, Dr. Warren was an examiner in diagnosis of the New York State Board of Medical Examiners from 1933 until his death, and was an active participant in the activities of many civic and educational organizations. He was a member of the Board of Trustees of Polytechnic Institute and of the Packer Collegiate Institute, a member of the Board of Directors of the Brooklyn Chamber of Commerce and Chairman of its Public Health Committee, President of the Brooklyn Health Council and Member of Board of Directors of the Brooklyn Council for Social Planning.

From 1911 onward Dr. Warren began to contribute to medical literature, his early works being devoted to clinical laboratory methods. He contributed a Section on Diseases of the Bronchi to Tice's Practice of Medicine and was Medical Editor of the International Medical Digest from 1920 to 1928. He was frequently called upon to speak or to discuss papers at medical meetings and always gave freely of his knowledge.

On reading of the foregoing list of activities of this remarkable man, one would conclude that here was a full-time professor in the medical school, with nothing to do but to teach, to administer his departments and to attend meetings. But this was decidedly not the case with Dr. Warren. His private practice was one of the largest in Brooklyn, and no one was called upon more for consultation work. He was worshiped by his students, and when they entered practice they constantly sought his help in difficult cases. He reported at the hospital at 8:30 every morning, worked all day and evening, and would often say that his only time for study and for preparation for his day's work would be between 12:00 and 3:00 a.m. Although slight of build he was a man of iron. His muscles were like whip-cords. He gloried in his farm at Brewster, New York, where he experimented with

DR. FRANK SMITHIES

MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

intensive production of crops and animals. He was a loving husband and father, taking particular delight in recounting the events of his children's educational and developmental life. He and Mrs. Warren were genial hosts and entered much into the social activities of Brooklyn. His daughter's debut was an event of importance in the city's social life.

Those associated with Dr. Warren in his many activities knew him as a man with high ideals, whose large brown eyes would glow and whose firm jaw would set with determination when he was advocating a measure which he considered to be right, or opposing one which he felt would be inadvisable or unjust. He not only worked hard himself, but had the faculty of making others exert themselves to the utmost, so that he lived constantly in an atmosphere of intense activity. It is no wonder that his life should have been ended so soon. He compressed a maximum of living into his 51 years of life.

A. F. R. ANDRESEN, M.D., F.A.C.P.

DR. FRANK SMITHIES

Dr. Frank Smithies (Master) passed away Tuesday morning, February 9, 1937, following a cerebral hemorrhage.

He was born in Elland, England, December 21, 1880, and came to the United States when a very young child and had his elementary school education in Philadelphia and Chicago. He was a graduate of the Calumet High School of Chicago and studied medicine at the University of Michigan, from which school he was graduated in 1904. Following this he went abroad and studied at the University of Berlin and Guy's Hospital, London.

After returning to this country he taught at the Rush Medical College 1904–05, and then at the University of Michigan, 1906–10. He then went to the Mayo Clinic, Rochester, Minn., where he was gastro-enterologist from 1911–14. After this he removed to Chicago, where he practiced diagnostic medicine with especial reference to diseases of the digestive system. From 1915 to 1925 he was professor of medicine at the University of Illinois. He was Attending Physician, Henrotin Hospital, since 1921; Chief of Clinic in Digestive Diseases, Municipal Tuberculosis Sanitarium, Chicago, 1927–30; Consulting Physician of the C. M. & St. P. R. R.

He made many contributions to the medical literature. His papers numbered well over one hundred, including his book on Cancer of the Stomach, published in 1916. He was Editor-in-Chief of the *American Journal of Digestive Diseases and Nutrition*, and Associate Editor of the *American Journal of Syphilis* (St. Louis) and *American Journal of Tropical Medicine* (Baltimore). He was the first Editor of the *Annals of Clinical Medicine*, official journal of the American College of Physicians.

He was past president of the following societies: American College of Physicians, 1927–28; American Gastro-Enterological Association, 1929–30; American Society of Tropical Medicine, 1931–32; American Therapeutic Society, 1932–33.

His hobbies were reading and fishing. He collected many rare books and was particularly interested in books on arctic explorations of which he had an unusually large collection.

In 1917 he was made a Fellow of the American College of Physicians, and elected a member of its Council later in the same year. In 1918, together with a group of prominent Internists throughout the country, the reorganization of the American College of Physicians was undertaken, with Dr. Smithies as Secretary General. The rapid advancement of the College from that time on was recognized as due, to a large extent, to the forceful presentation by Dr. Smithies of the great need for the organization by the Internists of America. He introduced the clinical character of its annual meetings, stimulating great interest in these gatherings. In recognition of service to the College, he was made one of the six Masters of the society, he being the fourth of these to pass away. He was liaison representative of French and American Medicine in this Country, and was made a Chevalier of the Legion of Honor of France.

A great soul has gone from us. Frank Smithies is no longer with us. In our hearts and minds we realize that we have sustained a major loss, the magnitude of which grows as we contemplate his achievements, his capacity of analytical ingenuity, his editorial versatility, his differential judgment, an outstanding gift of sympathetic understanding as well as a prophetic vision of the future of Internal Medicine. His virile spirit enabled him to surmount difficulties which would have halted less courageous souls.

CLEMENT R. JONES, M.D., F.A.C.P.

DR. LOUIS HENRY FALES

Dr. Louis Henry Fales (Fellow), Livermore, Calif., died February 13, 1937, at Fort Miley, San Francisco, of anemia.

Dr. Fales was born at Janesville, Wis., October 7, 1871. He received the degree of Bachelor of Laws from the University of Wisconsin in 1893 and the degree of Doctor of Medicine from Rush Medical College, Chicago, in 1897. He interned at St. Luke's Hospital, Chicago, 1897–99. He was Physician-in-Charge of the Bilibid Prison Hospital, Manila, P. I., 1901–03; Physician-in-Charge, Baguia Sanitarium, Baguia, P. I., 1903–04; in 1918 he was commissioned Captain in the Medical Corps of the U. S. Army, and was discharged in 1920. He also held a commission as past assistant surgeon in the U. S. Public Health Service and assigned to active duty in 1920.

He was commissioned surgeon in this Service in 1920. In 1924 he transferred to the U. S. Veterans Bureau. He served as ward surgeon and acting clinical director of the Veterans Administration Hospital at Palo Alto, Calif., 1924–25, and as ward surgeon, acting clinical director, medical officer in temporary charge and acting roentgenologist at the Veterans Administration Hospital, Livermore, Calif., between 1925 and the date of his death. In his earlier work in the Philippine Islands he was a medical inspector with the Philippine Health and Sanitary Service, and had considerable experience with bubonic plague and cholera at that time.

Dr. Fales was the author of a number of articles, appearing in leading medical journals. He was a past president of the Veterans Administration Facility Medical Society, a member of the Alameda County (Calif.) Medical Society and a member of the American Tuberculosis Association. In the course of his work he pursued various postgraduate courses at the University of Wisconsin, the U. S. Army Medical School and the University of California Medical School, always seeking to keep himself well informed of medical progress. He had been a Fellow of the American College of Physicians since 1933.

DR. WALTER OLIN NISBET

Walter Olin Nisbet, B.S., M.D., F.A.C.P., died suddenly in Charlotte, North Carolina, his home, January 18, 1937.

He was born in Lancaster County, South Carolina, October 5, 1866, the son of Dr. John Newton and Mary Jane Phifer Nisbet. He graduated at the University of South Carolina in 1885 with the B.S. degree, receiving his medical degree in 1889 from the Medical College of South Carolina in Charleston, serving his internship in the Roper Hospital in that city. He was a member of the S. A. E. and O. D. K. fraternities.

After ten years of general practice in Richburg, South Carolina, and Waxhaw, North Carolina, he spent a year in study in Berlin, preparatory to entering the field of gastroenterology, in which field he became recognized as one of the leading specialists of the South. He located in Charlotte, North Carolina, at this time, and was dean at the medical school there from 1912 to 1916. With others, he organized the Charlotte Sanatorium in 1909, and continued as a member of its staff as well as that of the Presbyterian Hospital until his retirement in 1934, two years after suffering a coronary occlusion.

Dr. Nisbet was for twenty-five years an elder of the Second Presbyterian Church, and was a member of the Charlotte Country Club, his chief interest in sport being in hunting and golf. He was a member of his County and State Medical Societies, the Tri-State Medical Society, the Southern Medical

Association, the American Medical Association, and the Gorgas Memorial Institute of Tropical Medicine, and he became a Fellow of the American College of Physicians in 1923.

His contributions in his chosen field were always well informed, illuminating, and authoritative. Ever alert to progress in his chosen line, he was particularly interested in the development and progress of his younger colleagues, all of whom as well as a host of friends throughout the South revere his memory. To them he was ever a source of comfort, strength, and friendly encouragement.

He is survived by his widow, the former Miss Eugenia Heath of Waxhaw, and three sons, Everett, Walter O. Jr., and Dr. Douglas Heath Nisbet, F.A.C.P, who was associated with him in practice for the past eighteen years.

CHARLES H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina.

DR. WILLIAM G. STEARNS

William Guilford Stearns was born at Lomactine, Wisconsin, February 11, 1865.

He attended Northwestern University Medical School from which he was graduated in 1893. The following year he served an internship at St. Luke's Hospital in Chicago, and the next year acted as Assistant Physician at the Illinois State Hospital for the Insane at Kankakee, Illinois; he served for two years in the same institution as Pathologist and later was the Medical Superintendent for two years. He was Medical Superintendent of the Oakwood and Lake Side Sanatoria, Lake Geneva, Wisconsin, from 1900 to 1904; Professor of Pathology, Anatomy, and General Pathology at Northwestern Dental School, 1894 to 1898, and Assistant Professor of Mental Diseases and Medical Jurisprudence at Northwestern University Medical School, 1898 to 1900. Later he served as Lecturer in Neurology at the College of Physicians and Surgeons in Chicago, 1900 to 1902. In 1898 he was Chairman of the Section on Insanity, National Conference of Charities and Correction. He served with the Medical Advisory Board, Number 3E Selective Service, as a consultant in neuro-psychiatry, 1917 to 1919. He was Medical Director of the North Shore Health Resort, Winnetka, Illinois, 1931 to 1936.

Dr. Stearns was a member of Nu Sigma Nu and Alpha Omega Alpha fraternities. His society memberships included American Medico-Psychiatric Association, Central Neuro-Psychiatric Association, Chicago Medical Society, Illinois State Medical Society, Chicago Neurologic Society, Chicago Society for Prevention and Relief of Heart Disease, Fellow of the

American College of Physicians (1917), American Medical Association and Chicago Institute of Medicine.

Dr. Stearns was recognized as a member of the profession, highly regarded by his fellow practitioners. His friends in and about Chicago, both professional and others, were legion. He was a man of upright character, noted for his fairness, integrity and good judgment and widely known as a gentleman of fine character, and a physician of unusual talents. The profession in Chicago has lost a man who was an exemplar of a type of character which brings to our profession special regard. He will be sorely missed by those who have had the privilege of knowing him personally.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

HISTORIC ST. LOUIS

LONG ago the site of St. Louis was peopled by the Mound Builders, a prehistoric race which inhabited the Mississippi Valley. Little is known about them, but it is interesting to note that the ancient Toltecs of Mexico had legends that their nation originally lived in and was driven from a country far away to the northeast. In the collections of the Missouri Historical Society are strange relics of a civilization believed to antedate the Indians and to have represented a superior race.

St. Louis is sometimes called the "Mound City," from the many strange mounds discovered on its site. The largest of these was at what is now Mound Street, at the corner of Broadway. Others were in the present Forest Park. Seven miles east of the city is the famous Cahokia, or "Monk's Mound," said to be the greatest in the world. This mammoth of the group is larger than the greatest Egyptian Pyramid, and appears to be much older. It is an earth pyramid 1,080 feet long, 780 feet wide and 104 feet high, spreading its huge bulk over 15 acres of ground, with terraces at various levels.

The origin of these mounds has long been shrouded in mystery. Warren King Moorehead, Curator of the Museum of Phillips Andover Academy, several years ago made a series of careful excavations and for six weeks peered into the mysteries of these great earth piles, obtaining therefrom much scientific data. He found proof that they were deliberately fashioned by man. It is probable that they were once the site of an ancient city whose population ran into the thousands—perhaps 100,000 persons—who lived and toiled and disappeared long before the beginnings of American chronicles.

The founding of the present city must be attributed to a far-sighted French merchant, named Pierre Laclede Liguest, who conceived the idea of establishing a permanent settlement in some favorable location on the Mississippi. Accompanied by young Auguste Chouteau, he explored the river searching for an ideal spot. In December, as the still preserved record relates, "he fixed upon the place, marked with his own hands some trees and said to Chouteau, 'You will come here as soon as navigation opens and will cause this place to be cleared in order to form our settlement after the plan I shall give you,' and to DeNoyon, Commandant at Fort Des Chartres, he enthusiastically stated that he had found a situation where he was going to form a settlement which might become, hereafter, 'one of the finest cities in America—so many advantages were embraced in this site, by its locality and its central position for forming settlements.'"

It was on the evening of February 14, 1764, that Chouteau and a band of thirty French pioneers landed on the west bank of the Mississippi River at what is now the foot of Walnut Street in St. Louis. For four long days they had poled and dragged their heavy craft from Fort Chartres, sixty

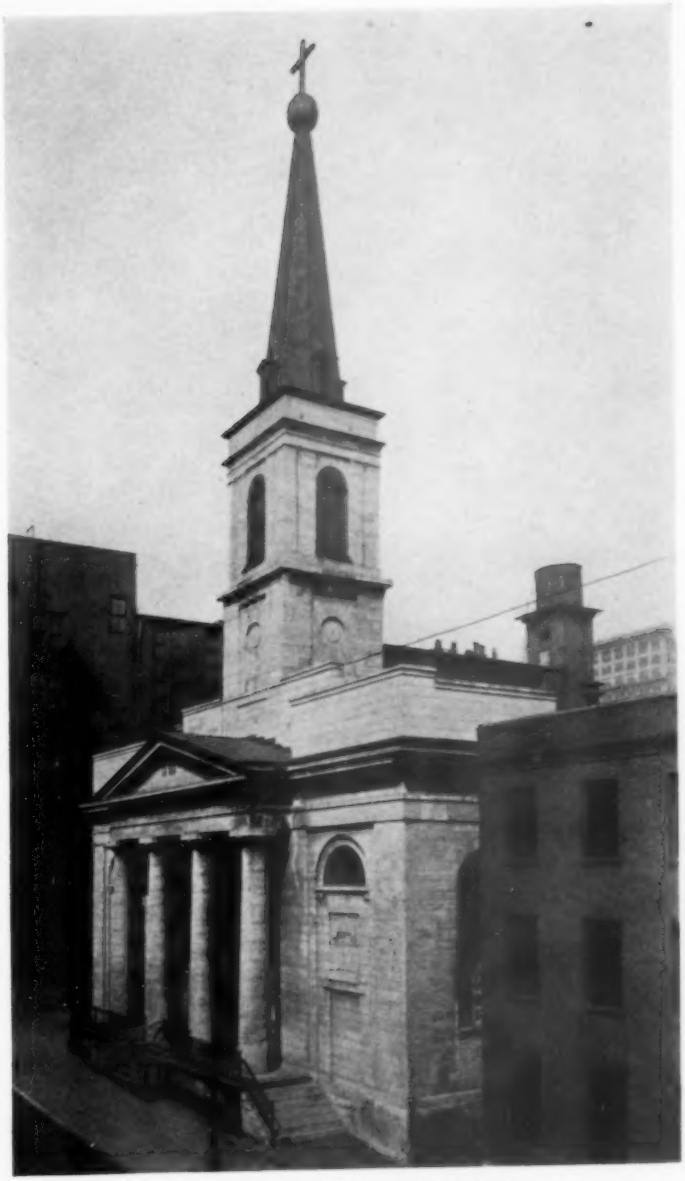


FIG. 1. Old St. Louis Cathedral.

miles below. Wearied by their labors, they slept that night in the boat. On the following morning Chouteau led his men across the sandy beach, up to the plateau overlooking the river and pointed out to them the line of trees which he and Laclede had marked. Thus began the building of St. Louis.

Those were pioneer days. The entire upper Mississippi Valley was a silent wilderness. Here and there, hundreds of miles apart, were roughly stockaded and scantily garrisoned forts and trading posts, constituting the meager outposts of civilization, the sole refuge against Indian attacks. Life was a continued struggle for existence.

Other expeditions, French and Spanish, soon sought to overshadow the little settlement of St. Louis. A Spanish Fort was built a short distance to the north. Yet so well had Laclede chosen, and so energetically had his followers labored, that these competitive efforts gradually merged with St. Louis itself. Within three years its colonists had established valuable fur-trading monopolies with the 28 principal Indian nations, including not only those west of the Mississippi, but also east of the river and even as far north as the Great Lakes. These the English tried in vain for many years to break.

The fur trade was the commercial cornerstone of St. Louis' prosperity. Every year saw the city's sphere of influence broaden. Up the Mississippi and Missouri crept a line of outposts. St. Louis became the gateway of a stream of migration, the starting point of expeditions in all directions, some military, some scientific, others to establish new communities or to open commercial avenues. The greatest of these, the Lewis and Clark expedition, which was responsible for the opening of the Northwest, left St. Louis in 1804. The Frenchmen of St. Louis paved the way for the American occupation of Louisiana. A branch of the Chouteaus started Kansas City. Robidoux, of St. Louis, established St. Joseph. One of the Menards founded Galveston. A hundred western cities and towns owe their beginning to St. Louisans.

The Sights of St. Louis

No visitor to St. Louis should be at a loss as to what to do or what to see. Members of the medical profession and their wives who visit St. Louis in April will enjoy the Art Museum, the Cahokia Mounds, the Confederate Memorial, the Dent House, Forest Park, Grant's Log Cabin, the Jefferson Memorial, the Lindbergh Trophies, the Old Court House, the Mississippi River Front, Shaw's Gardens, St. Louis Municipal Airport, the Zoölogical Gardens and many other attractions.

The St. Louis Zoo is worthy of special attention. Feeding time in the midafternoon is an event of interest and pleasure for young and old. The trained chimpanzees, the monkey kindergarten, the performing tigers and the hungry, barking sea lions constitute a show which will long be remembered. The collection of reptiles, now housed in a new and beautiful build-

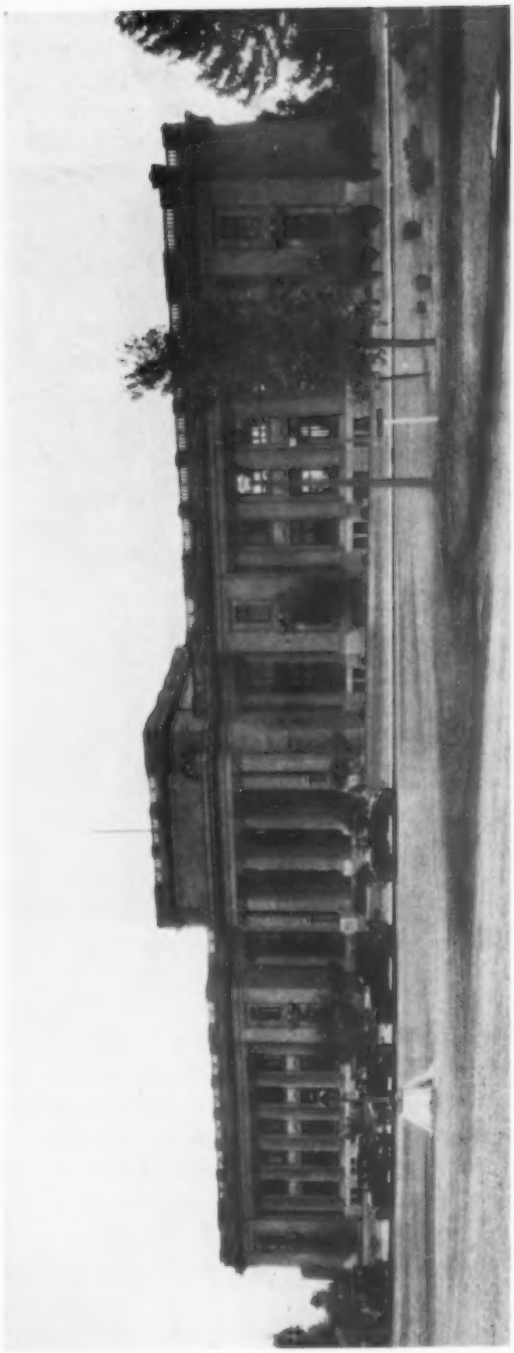


FIG. 2. The Jefferson Memorial which houses the Records of the Missouri Historical Society and the Lindbergh trophies.

ing, is outstanding. The cageless bear pits, which have attracted the notice of zoölogical experts from all over the world, are artificial rocky dens with earth filled fissures from which grow native shrubs and evergreens. This unique method of exhibiting wild animals has proved so satisfactory that similar accommodations have been provided for many other creatures in the zoo.

After visiting the Zoölogical Gardens one should see the Jefferson Memorial, an imposing marble structure which stands on the site of the main entrance of the World's Fair of 1904. Here one can see relics of the Mound Builders, curios of the Indian tribes who traded with the founders of St. Louis, original manuscripts of the French and Spanish days in Missouri, relics of the pioneers and of the Revolutionary, Mexican, Spanish-American and World Wars. In addition to the third largest collection of Jefferson manuscripts, the Jefferson Memorial holds a large part of the original documents of the Hamilton-Burr controversy, which culminated in the death of one brilliant man and the destruction of the career of another. In the display cases many of the manuscript records of the Lewis and Clark Expedition may be seen.

Of supreme interest today is the complete showing of the famous Lindbergh Collection, including gifts, medals, trophies and souvenirs from a score of foreign countries and from thousands of sources. These have been viewed by more than 5,000,000 persons since they were put on exhibit. From 500 to 1200 people call to see these trophies daily. Colonel Lindbergh recently deeded to the Missouri Historical Society custody of the hundreds of mementos which have come to him in connection with the epoch-making flight of the "Spirit of St. Louis" across the Atlantic, and his friendship tour to the countries of Mexico, Central and South America.

St. Louis' Art Museum, erected during the World's Fair of 1904 as a permanent building, stands on the crest of Art Hill in Forest Park, overlooking the West End residential district and the suburbs which stretch out to the north and west. To its immediate foreground is a vista of sloping landscaped lawn, of glimmering lake and of speeding motor-cars on the winding drives beyond. No other museum building in America has a setting of such natural splendor. This great treasure-house of art is open daily, free to all. Ranked as one of the four best art galleries in the United States, the Museum contains rich exhibits of paintings, casts, sculpture, marble, drawings, architecture and applied art. Many rare canvases, the work of the old masters, are here. Its collection of Chinese bronzes, ceramics and paintings is one of the finest of its kind. Visitors will be especially interested in the period rooms and in the remarkable carved outdoor staircase from Morlaix, in Brittany. St. Louis is one of the few cities in the United States which fosters the development of artistic and cultural facilities for the public by a direct tax for the maintenance and development of its Art Museum, thereby making superior advantages of this kind available to everyone.

During a visit to Forest Park one should not miss a glimpse of the famous Jewel Box, a rare and artistic display of flowers and other plants held regularly in the city's greenhouses located in Forest Park. Thousands of persons annually visit the splendid displays arranged there.

FIG. 3. Art Museum.

Entirely separate from the Jewel Box is the Missouri Botanical Garden. Founded in 1860 by Henry Shaw, a St. Louis philanthropist, it is popularly known as Shaw's Garden, and ranks second only to the famous Kew Gardens of England. It contains the largest collection of plant life in the western hemisphere and is famous the world over for its wealth of botanical species and its beautiful floral displays. It comprises a city garden of about 75 acres, an out-of-town extension of more than 1,625 acres, and a tropical extension at Balboa, Panama.

At the city garden large conservatories are maintained, containing a varied collection of tropical plants and providing for an almost continuous display of chrysanthemums, orchids, lilies, tropical vines, ferns, palms, Australian, Philippine and Japanese plants, desert cacti and other growing plants. Out of doors are to be found representative gardens of roses, irises, water

lilies, and collections of every other kind of plant which can be grown in the region of St. Louis. The orchid and chrysanthemum shows have established national reputations for the gorgeousness and rarity of their blooms and for the beauty and method of their display. Altogether, more than 11,000 species of plants from all climes and all parts of the globe are to be seen here.

FIG. 4. The Jewel Box in Forest Park.

One of the best botanical libraries in the country, one of the largest herbaria in the United States, laboratories for scientific work and a school for gardening combine the features of a pleasure-ground with the facilities of an institution of research.

The out-of-town garden, which is constantly being developed, is already one of the best localities in the state for the growing of wild flowers and trees. The propagation of rare and delicate plants away from conditions unfavorable to early plant life incident to a city location is carried on there. Besides growing much material for later exhibit in the city garden, there is gradually being developed an adequate arboretum, which in time will probably become the most complete reservation for trees and native flora in the temperate zone.

Medical St. Louis

The St. Louis Medical Society was founded in 1836 by a small group of physicians and until 1850 was known as the Medical Society of the State of Missouri. At that time the Missouri State Medical Society was organized, and the name of the local organization was changed to the St. Louis Medical Society.

Fig. 5. St. Louis Medical Society.

In the early days the meetings were held in the assembly room of the Public School Library in the Polytechnic Building, then on Seventh and Chestnut Streets, and later a room in the Y. M. C. A. was used.

The excellent library of the St. Louis Medical Society is an outgrowth of the St. Louis Medical Library Association, formerly known as the Medical Exchange Journal Club. The St. Louis Medical Society moved into its beautiful new $400,000 home at 3839 Lindell Boulevard on July 29, 1926. This building was planned and constructed especially for the convenience and comfort of the physicians of St. Louis. It contains an auditorium which has a seating capacity of seven hundred, and several private meeting rooms, a dining room and adjoining rooms for entertainment.

On the walls of the first floor lobby there are tablets of Bernard Farrar, the first president of the St. Louis Medical Society; William Beaumont, the pioneer American physiologist, who was president of the Society in 1841; and John Thompson Hodgen, well-known St. Louis surgeon, who was president of the Society in 1876.

The library occupies the entire second floor and contains more than 30,000 volumes with 325 files of current journals and transactions in

English, French and German. A valuable collection of rare old medical books numbering about 800 volumes, with pictures of medical historical interest, was given to the Society by the late James Monroe Ball and is exhibited in one of the rooms on the second floor in connection with the library.

The Bartscher room is a memorial to Dr. Hugo Bartscher from his mother, Mrs. Franciscus Bartscher. It houses many valuable historical collections, rare old medals and books, art exhibits and an excellent display of unusual photography, the work of members. On the walls are several plaques of prominent members donated by their friends in appreciation and commemoration of their valuable service to the Society. The Society has 1,000 active members. Weekly scientific meetings are held in the auditorium. The organization publishes its own weekly bulletin carrying

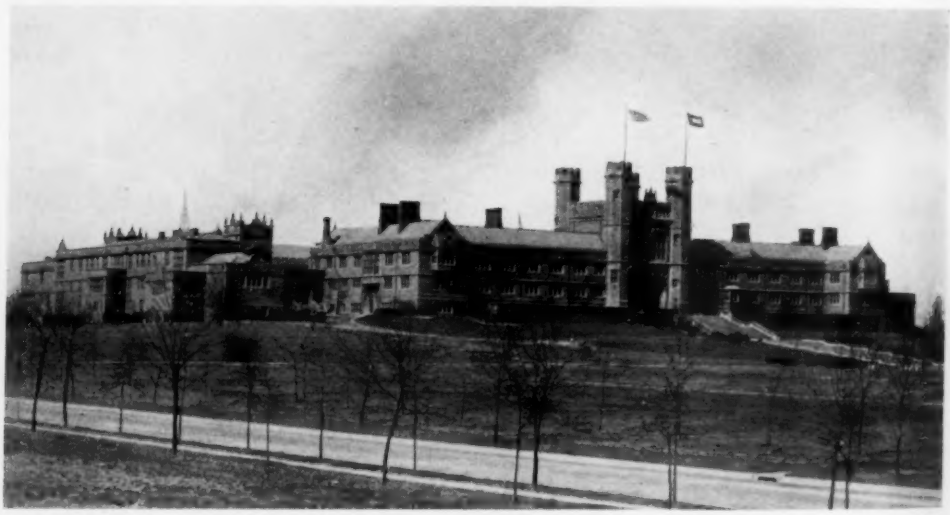


FIG. 6. St. Louis University Medical School.

the news of the Society, keeping its members informed as to the programs, local public health statistics, and medical news, including the proceedings of the meetings and scientific papers.

For more than three years the Society has sponsored, edited and broadcast weekly radio talks pertaining to public health matters over one of the local broadcasting stations. During the fifteen-minute program allotted through the courtesy of the station, diseases of common interest are discussed, the name of the editor and speaker being withheld. More than 170 radio talks have been broadcast.

St. Louis University School of Medicine. The School of Medicine of St. Louis University was established in 1837 in a small house on Washington Avenue between Tenth and Eleventh Streets. In 1847 the school was moved to its own college building on Seventh and Clark Avenues. The

affiliation between the medical school and the University was severed in 1855, and the medical department became known as the St. Louis Medical College and functioned as an independent school.

The Marion Sims College of Medicine, founded in 1890 and occupying a building erected for the purpose on Grand Boulevard and Caroline Street, combined in 1901 with the Beaumont Medical College, organized in 1886, and became known as Marion Sims-Beaumont Medical College. In 1903 the University assumed control of these schools, which had been merged two years previously, and became known as the St. Louis University School

Fig. 7. The Firmin Desloge Hospital associated with St. Louis University Medical School.

of Medicine. In the reorganization which ensued the fundamental departments, anatomy, chemistry, physiology, pathology, bacteriology and pharmacology, were placed under the direction of full-time departmental heads.

The main building of the original Marion Sims College of Medicine was used until 1927, when the present medical buildings were erected. The buildings are located on Compton Hill, one of the highest points in the City of St. Louis, the main building facing Grand Boulevard at Caroline Street.

An excellent medical library, which has been enriched by several private collections, is housed in the south wing of the building.

The University Hospital, affording clinical teaching facilities to the Medical School, embraces a group of three hospitals: the Firmin Desloge Hospital, St. Mary's Hospital and Mt. St. Rose Sanitarium. The Sisters of St. Mary have placed their educational and medical activities in these institutions under the complete control of the University. By an agreement between the Sisters and the University, the Directors of the various departments of the School of Medicine are made responsible for the corresponding hospital departments, thus forming a compact organization, assuring the

FIG. 8. St. Luke's Hospital.

closest university supervision and the highest type of medical, educational and nursing efficiency.

The Alexian Brothers', St. Anthony's and St. John's Hospitals are known as the "Associated Hospitals." These hospitals afford further teaching facilities and in return are given leadership and guidance in their medical and educational activities. The staffs are appointed by the University.

Intimate association is also maintained among the St. Ann's Lying-In Infirmary, St. Ann's Founding Society and the St. Louis Obstetric Dispensary. These institutions are utilized as teaching centers for obstetrics

and pediatrics. Opportunity is also afforded for teaching in the St. Louis City Hospital, Isolation Hospital and St. Louis City Sanitarium.

Washington University School of Medicine. St. Louis Medical College, founded in 1842, was admitted as a department of the University in 1891. In 1899 the Missouri Medical College, which was founded in 1840, was united with the St. Louis Medical College to form the medical school of Washington University. This school therefore continues the work of the St. Louis Medical College and the Missouri Medical College, two of the oldest medical schools west of the Mississippi River.

FIG. 9. Jewish Hospital.

In 1910, the corporation of the University, appreciating the valuable service which a medical school can render to the community, with the co-operation of the medical faculty, reorganized the school in all departments and appointed heads of departments and instructors in anatomy, physiology, biological chemistry, pathology, medicine, surgery and pediatrics, who devote themselves to teaching and research. Associated with this staff are many clinical instructors chosen from the medical profession of St. Louis.

In 1914 the Washington University School of Medicine moved from its old location on the corner of Eighteenth and Locust Streets to the new buildings facing Forest Park on the corner of Kingshighway Boulevard and Euclid Avenue. The buildings of the School of Medicine form a part of a medical group known as the Barnes Hospital group.

The affiliation of Barnes Hospital, St. Louis Children's Hospital, St.

Louis Maternity Hospital, McMillan Eye, Ear, Nose and Throat Hospital, Mallinckrodt Radiological Institute, and Oscar Johnson Institute with Washington University School of Medicine makes these institutions for teaching purposes integral parts of the School of Medicine.

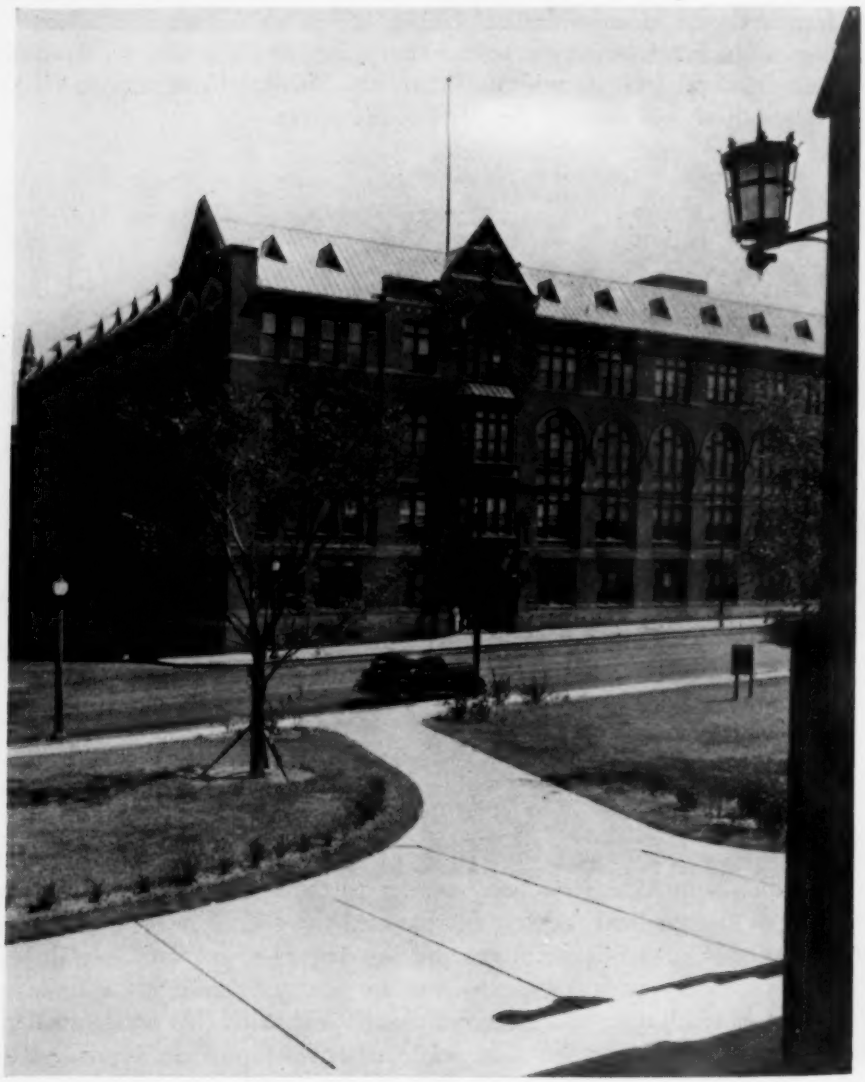


FIG. 10. Washington University.

The Washington University Clinics serve as an out-patient department for the University group of hospitals.

Further teaching facilities are afforded by the St. Louis City Hospital, including the Isolation Hospital and the City Sanitarium.

FIG. 11. The Medical Center at Washington University, including Barnes Hospital, St. Louis Children's Hospital, St. Louis Maternity Hospital, McMillan Hospital, Oscar Johnson Institute and Mallinckrodt Institute of Radiology.

FIG. 12. St. Louis City Hospital.

An excellent library is housed in the Medical School and several museums and collections for teaching and investigation are maintained by the various departments. Recently a valuable collection of anatomical specimens prepared with unusual skill and care by Bohumil Hochmann has been purchased for the museum. Diseases of bones are well illustrated by a large number of specimens collected during the early history of the school by Dr. Charles A. Pope and Dr. John T. Hodgen. A section of the museum contains experimental pathological lesions.

The Beaumont Room, adjoining the main reading room of the library, contains manuscripts, letters and other valuable material of the pioneer American physiologist, William Beaumont, presented to the University by his granddaughter, the late Lily Beaumont Irwin. One of the interesting items in this collection is the memorandum book containing Beaumont's original notes of the accident which befell Alexis St. Martin and made possible the renowned investigations in gastric digestion.

Independent Hospitals. The hospitals which are directly connected with the two schools of medicine have already been briefly mentioned. There are numerous other excellent hospitals in St. Louis but space does not permit details concerning their many prominent features. Among these independent hospitals are the Barnard Free Skin and Cancer Hospital, Bethesda Hospital, Christian Hospital, DePaul Hospital, Evangelical Deaconess' Home and Hospital, the Frisco Employees' Hospital, Jewish Hospital, Lutheran Hospital, Missouri Baptist Hospital, Missouri Pacific Hospital, St. Ann's Widows' Hospital, St. Louis City Hospital No. 1, St. Louis County Hospital, St. Luke's Hospital, Shriners' Hospital and United States Marine Hospital.

PROGRAM
TWENTY-FIRST ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
ST. LOUIS, MISSOURI

April 19 to 23, 1937

GENERAL SESSIONS

Ernest B. Bradley, President

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David P. Barr, Chairman

Louis H. Behrens
Jerome E. Cook
Ralph A. Kinsella
Alphonse McMahon
Elsworth S. Smith

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Harry L. Alexander
Walter Baumgarten
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Llewellyn Sale
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Hiram S. Liggett
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COMMITTEE ON PUBLICITY

Jerome E. Cook, Chairman

Lee D. Cady — Alfred Goldman

Charles E. Gilliland

WOMEN'S COMMITTEES

Entertainment Committee

Mrs. O. P. J. Falk, Chairman

Mrs. David P. Barr — Mrs. Frank D. Gorham

Mrs. Walter Baumgarten — Mrs. Elsworth S. Smith

Mrs. Horace W. Soper

Registration Committee

Mrs. Ralph A. Kinsella, Chairman

Mrs. Lee D. Cady, Co-Chairman

Mrs. Anthony B. Day — Mrs. Charles H. Neilson

Mrs. William W. Graves — Mrs. LeRoy Sante

Mrs. Joseph W. Larimore — Mrs. August A. Werner

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Mrs. Harry L. Alexander, Chairman

Mrs. Llewellyn Sale, Co-Chairman

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Mrs. Jerome E. Cook — Mrs. James F. McFadden

Mrs. Lee Pettit Gay — Mrs. James R. Nakada

Mrs. Charles E. Gilliland — Mrs. Howard A. Rusk

Mrs. Alfred Goldman — Mrs. Edwin J. Schisler

Mrs. Hiram S. Liggett — Mrs. Jacob Jesse Singer

Mrs. John Zahorsky

INVITATION

The City of St. Louis, the St. Louis Medical Society, the Medical Colleges of St. Louis and of Washington Universities have through their officers extended to the Fellows of the American College of Physicians a most cordial invitation to hold their 1937 Annual Session in St. Louis. The great hospitals of the City have offered their lecture halls, laboratories and wards for demonstrations and clinics. Members of the local medical profession have signified their willingness and desire to aid in the programs which have been arranged for each morning of the session.

With its two large medical schools and its numerous general and special hospitals, St. Louis offers admirable facilities for the meeting. Indeed, there are so many that it has been found impossible or at least unwise to use all of those which were made available to the committees. Consequently, the greater part of the clinical programs is to be held in only four centers: in St. Luke's Hospital, in the Jewish Hospital, and in the institutions which are associated with the two medical schools. In its teaching, St. Louis University embraces a group of hospitals which includes St. Mary's Hospital, the Mount St. Rose Sanitarium, the Alexian Brothers', St. Anthony's and St. John's Hospitals, and the beautiful new and modern Firmin Desloge Hospital, where many of the meetings will be held. Washington University is closely affiliated with the Barnes Hospital, St. Louis Children's Hospital, St. Louis Maternity Hospital, McMillan Eye, Ear, Nose and Throat Hospital, the Mallinckrodt Radiologi-

cal Institute, and the Oscar Johnson Institute, the whole forming a medical and health center of outstanding importance. The facilities of the Barnes Hospital will be chiefly used for the meetings.

Many of the scientific discussions and clinics will be contributed by the members of the medical profession of St. Louis. Several distinguished guests, and a few of the outstanding Masters and Fellows of the College from other cities have been asked and have graciously consented to aid in the programs. While there has been scheduled each day a large number of formal programs, it is hoped that the visiting Fellows will find time to view informally the activities in the research laboratories and the points of special interest in the hospitals and medical schools. Among things which should attract particular attention are the Beaumont room of the Library at Washington University School of Medicine, which contains manuscripts, letters and other valuable original material of the pioneer American physiologist, William Beaumont, and the collection of anatomical specimens prepared by Bohumil Hochmann and housed in the museum of the anatomical department at Washington University.

St. Louis also offers to the visitor many attractions other than those of a medical and scientific nature. Among these may be mentioned the world famed Missouri Botanical Gardens, the Art Museum, the St. Louis Zoo, and the Lindbergh Trophies.

It is the sincere hope of the local committees that the St. Louis Session may be memorable among the many enjoyable and profitable meetings of the College.

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1937 (dues, if not paid previously, may be paid at the Registration Bureau).
(*b*) All newly elected members.
(*c*) Members of the St. Louis City Medical Society, without registration fee, upon presentation of their 1937 membership cards.
(*d*) Medical students pursuing courses at the St. Louis University School of Medicine and the Washington University School of Medicine, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions; exhibits, morning lectures and general sessions.
(*e*) House officers of the hospitals participating in the program, upon presentation of proper identification; exhibits, morning lectures and general sessions.
(*f*) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
(*g*) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU.—Temporary Registration Bureau will be open at the Jefferson Hotel on Sunday afternoon and evening, April 18. The permanent Registration Bureau will be located on the mezzanine floor of the Jefferson Hotel. Hours: 8:30 a.m. to 6:00 p.m., daily, April 19 to 23.

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS, MORNING LECTURES AND ROUND TABLE CONFERENCES will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

GENERAL INFORMATION

Headquarters

Jefferson Hotel, 12th and Locust Sts.

The Jefferson Hotel will be headquarters for Officers, Regents, Governors and members of the College; also the general headquarters for registration, technical exhibits, general scientific sessions, special lectures and round table conferences.

List of St. Louis Hotels	No. of Rooms	Blocks Removed from Headquarters	RATES PER DAY				
			ROOM—ONE PERSON		ROOM—TWO PERSONS		
			With Bath	Without Bath	With Bath	Without Bath	Suites
Jefferson Hotel, 12th and Locust	800	..	$3.00–5.00 *	.....	$4.00–7.00	.....	$5.00–8.00–12.00
Chase Hotel, Lindell and Kingshighway	500	38	3.00–4.50	.....	4.00–7.00	.....	10.00–20.00
Congress Hotel, 275 N. Union Blvd.	524	40	.....	.....	5.00–6.00	.....	6.00 up (Apts.)
Coronado Hotel, Spring and Lindell	700	25	2.00 up	.....	3.50 up	.....	6.00 up
De Soto Hotel, 1014 Locust	300	1	2.00–3.00	$1.50	3.00–4.00	$2.50	.....
Forest Park Hotel, Euclid and W. Pine	388	37	2.50 up	.....	4.00 up	.....	6.00–10.00
Kingsway Hotel, Kingshighway and W. Pine	270	39	2.00 up	1.50	3.00 up	.....	5.00 up
Lennox Hotel, 9th and Washington	400	4	2.50 up	.....	4.00–6.00	.....	.....
Mark Twain Hotel, 8th and Pine	300	6	2.50–3.50	.....	3.50–5.50	.....	6.00–10.00
Marquette Hotel, 18th and Washington	400	7	2.00 up	1.00–1.50	3.00 up	2.00–2.50	.....
Maryland Hotel, 205 N. 9th	250	5	2.00–2.50	1.50	3.00–3.50	2.50	.....
Mayfair Hotel, 8th and St. Charles	400	4	2.50–4.50	.....	4.00–7.00	.....	.....
Melbourne Hotel, Grand and Lindell	358	24	2.50–4.00	.....	4.00–7.00	.....	6.00–9.00
Park Plaza Hotel, 220 N. Kingshighway	1100	39	3.50 up	.....	5.00 up	.....	.....
Statler Hotel, 9th and Washington	650	3	2.50–5.00	.....	4.50–9.00	.....	12.00
Warwick Hotel, 15th and Locust	190	3	1.50	.....	2.50–3.00	.....	.....
York Hotel, 8 S. 6th	200	10	1.50 up	.....	2.50 up	.....	.....

* Also large rooms with bath for 3 or 4 persons at $1.50 per person.

BULLETIN BOARD FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Jefferson Hotel.

TRANSPORTATION.—On account of recent nation-wide reductions in railroad fares, convention rates are no longer in effect. In a great many instances, however, reduced round trip tickets are in effect from certain localities. Members should consult their local ticket agents.

Special service will be available to physicians from Chicago over the Alton Railroad and from the East (New York City, Philadelphia, Wilmington, Baltimore, Washington, Martinsburg, Parkersburg, and intervening points) over the Baltimore & Ohio Railroad. Special time-tables may be obtained from the Executive Secretary, or by application to local agents of the above railroads.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5:05 p.m., Thursday, April 22, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. James H. Means, Boston, Mass.

BOARD AND COMMITTEE MEETINGS.—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *special dinner* will be tendered *to the Board of Governors* by members of the Board of Regents at the Jefferson Hotel, Sunday evening, April 18. An announcement of the time and place will be made later. Members of the Board of Governors are cordially invited.

COMMITTEE ON CREDENTIALS

Sunday, April 18, 9:00 a.m. ..... Room 4, Second Floor, Jefferson Hotel

BOARD OF REGENTS

Room 4, Second Floor, Jefferson Hotel

Sunday, April 18, 2:30 p.m.
Tuesday, April 20, 12:00 m.*
Friday, April 23, 12:00 m.*

BOARD OF GOVERNORS

Room 4, Second Floor, Jefferson Hotel

Monday, April 19, 5:00 p.m.
Wednesday, April 21, 12:00 m.*

* Buffet luncheon served.

SPECIAL FEATURES

Monday, April 19, 1937

THE ANNUAL SMOKER will be given immediately following the scientific program about 10:20 o'clock in the evening in the Gold Room of the Jefferson Hotel. An interesting and amusing program has been arranged.

Wednesday, April 21, 1937

CONVOCATION OF THE COLLEGE.—8:15 p.m., Gold Room, Jefferson Hotel. All Masters and Fellows of the College and those to be received in Fellowship

should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in Rooms 8 and 9, second floor (next floor above mezzanine), of the Jefferson Hotel at 7:30 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Ballroom, to which they will be conducted by the Convocation marshal promptly at 8:15. As this is the most formal meeting of the College, it is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

Following the Convocation Ceremony, the President will present the John Phillips Memorial Medal for 1936–37. Thereafter will follow the Convocational Oration, "The Organism As a Unity," by Dr. John Dewey, Professor Emeritus of Philosophy, Columbia University, New York City.

The Presidential Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

TRUDEAU CLUB LUNCHEON.—The Trudeau Club of St. Louis cordially invites members of the College who are especially interested in diseases of the chest to attend a luncheon at the Park Plaza Hotel at 12:30 p.m. on Wednesday, April 21. This will be combined with a round table discussion to be conducted by Dr. James Alex. Miller. Because of the size of the dining room, attendance must be limited to 100. Those desiring to attend should obtain the special Round Table ticket, IV, by advance application or at the Registration Desk before Tuesday noon.

Thursday, April 22, 1937

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Gold Room of the Jefferson Hotel at eight o'clock. All members of the College, physicians of St. Louis, and visitors attending the Session with their families are cordially invited. Dr. Alfred Stengel will act as Toastmaster and Dr. Logan Clendening will deliver an address on "Medical Shrines." Following the banquet will occur the annual dance, to which all are invited to stay.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The headquarters of the visiting women will be in the Ladies Lounge on the mezzanine floor of the Jefferson Hotel. A program of special features has been arranged, but ample time has been allowed for sightseeing, shopping and recreation. Lists including the names of principal shops and restaurants will be issued by the local committee.

Monday, April 19, 1937

Morning: Registration.

Afternoon: 1:30 p.m. A personally conducted sightseeing tour to points of interest in St. Louis, to Old Cathedral, Shaw's Gardens, Lindbergh Trophies, and to the St. Louis Art Museum, where Tea will be served.

Tuesday, April 20, 1937

Afternoon: 3:00 p.m. Fashion Show and Tea at the Junior League Club. Cars leave Jefferson Hotel at 2:30

Evening: 8:00 p.m. Bridge, Jefferson Hotel.

WEDNESDAY, APRIL 21, 1937

Afternoon: 1:00 p.m. Luncheon and Bridge at the St. Louis Country Club. Cars leave Jefferson Hotel at 12:15.

Evening: 8:00 p.m. Convocation of the College in the Gold Room at the Jefferson Hotel. All ladies are cordially invited to attend.

THURSDAY, APRIL 22, 1937

Afternoon: 4:00 p.m. Tea given by the Woman's Club of the St. Louis University School of Medicine at the residence of Mrs. Cyrus Burford.

Evening: 8:00 p.m. The Annual Banquet of the College.
10:00 p.m. Dancing.
Gold Room, Jefferson Hotel.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the mezzanine floor of the Jefferson Hotel.

The exhibit will be particularly representative of the interests of Internal Medicine, and will include medical literature and texts, pharmaceutical products, apparatus and appliances, specialized physicians' furniture and many other items of special interest. These exhibits will afford an opportunity for physicians to keep informed of the latest literature and the newest products in the field of medicine generally; the educational value of these exhibits should never be overlooked. Furthermore, exhibitors contribute much not only to the interest of the meeting, but to the financial support of these scientific assemblies. Many exhibitors have nothing to sell, but merely seek an opportunity to show what their organizations are attempting to furnish for medical science. Every doctor is urged to visit each of the booths, for he will certainly find something new, interesting and scientifically valuable. Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

TECHNICAL EXHIBITORS

(Assignments up to February 10, 1937)

	Space
Allison Company, W. D., Indianapolis, Ind.	96–97
Aloe Company, A. S., St. Louis, Mo.	72–73
American Hospital Supply Corporation, Chicago, Ill.	17
Appleton-Century Company, D., New York, N. Y.	7
Arlington Chemical Company, The, Yonkers, N. Y.	8
Ayerst, McKenna & Harrison (United States) Limited, Montreal, Que.	62
Aznoe's National Physicians' Exchange, Chicago, Ill.	16
Baum Co., Inc., W. A., New York, N. Y.	37
Becton, Dickinson & Co., Rutherford, N. J.	22–23
Bilhuber-Knoll Corporation, Jersey City, N. J.	29–30
Borden Company, The, New York, N. Y.	88
Burdick Corporation, The, Milton, Wis.	80–81
Cambridge Instrument Co., Inc., New York, N. Y.	70
Cameron Surgical Specialty Company, Chicago, Ill.	31–47
Chappel Laboratories, Rockford, Ill.	15
Ciba Co., Inc., New York, N. Y.	38–39
Collins, Inc., Warren E., Boston, Mass.	51
Davies, Rose & Co., Ltd., Boston, Mass.	52
Davis Company, F. A., Philadelphia, Pa.	46

GENERAL SESSIONS

Ballroom, Jefferson Hotel, St. Louis, Mo.

In addition to the program for the General Sessions, attention is called to the Morning Lectures and to the Round Table Discussions. The programs for these two

OUTLINE OF SESSION

TIME	MONDAY	TUESDAY		WEDNESDAY		THURSDAY		FRIDAY	
	April 19	April 20		April 21		April 22		April 23	
9:00 a.m. to 12:00 m.	Morning free. Registration, Exhibits, etc.	1st Clinical Session	Morning Lectures (9:30–11:30)	2d Clinical Session	Morning Lectures (9:30–11:30)	3d Clinical Session	Morning Lectures (9:30–11:30)	4th Clinical Session	Morning Lectures (9:30–11:30)
12:00 m. to 1:00 p.m.		Round Table Conferences		*Round Table Conferences		Round Table Conferences			
1:00 p.m. to 2:00 p.m.	Luncheon	Luncheon		Luncheon		Luncheon		Luncheon	
2:00 p.m. to 5:30 p.m.	**1st General Session**	**3d General Session**		**5th General Session**		**6th General Session** Annual Business Meeting		**7th General Session**	
5:30 p.m. to 8:00 p.m.	Dinner	Dinner		Dinner					
8:00 p.m. to 11:00 p.m.	**2d General Session** followed by Smoker	**4th General Session**		Convocation, followed by President's Reception		ANNUAL BANQUET and Dance			

Morning Lectures, Round Table Conferences and General Sessions will be held at Jefferson Hotel, except: * Park Plaza Hotel, beginning at 12:15, Round Table 4.

features are arranged to supplement the presentations given in the General Sessions. A few of the programs are arranged in the form of symposia while in others no attempt has been made to follow this plan. Some subjects have been discussed intensively—these include:

Diabetes and the use of *Long-Acting Insulins, Endocrine Disturbances, Cardiovascular Diseases,* with especial reference to *Arterial Hypertension.*

Infectious Diseases are given a prominent place with the newer methods of treatment of *Streptococcal Infections.*

In addition the program offers presentations on

Medical History, Neurology, Gastro-enterology, Diseases of the *Bone Marrow, Hodgkin's Disease* and *Hypertrophic Arthritis. Nutritional Disturbances* as they affect the *heart* and *thyroid* are considered.

Syphilis is discussed from its *Public Health Aspect* and A Round Table discussion on its *Treatment* is provided.

Thyroid Disease in the negro is discussed and there are miscellaneous papers concerned especially with *Medical Treatment.*

The Convocational Oration will be delivered by Dr. John Dewey, Emeritus Professor of Philosophy at Columbia University. Dr. Dewey is America's foremost philosopher. He has best understood how the problems of modern life should be stated. His philosophy is a philosophy for daily use and is congenial to those attitudes that are taken instinctively by students of biology and physiology. His subject, "The Organism as a Unity," touches a point of acute interest today, the question, "What shall be the physician's attitude toward the soul-body problem, how shall there be better understanding between internist and psychiatrist?"

FIRST GENERAL SESSION

Monday afternoon, April 19, 1937

p.m.

2:00 Addresses of Welcome:
George R. Throop, Chancellor of Washington University.
Rev. Alphonse Schwitalla, S. J., Dean of Faculty of Medicine, St. Louis University.
Curtis H. Lohr, President of the St. Louis Medical Society.
Joseph F. Bredeck, Commissioner of Health, City of St. Louis.
Response to Addresses of Welcome:
Ernest B. Bradley, President of the American College of Physicians.

2:30 The Nature and Treatment of Heart Failure.
George R. Herrmann, Galveston, Tex.

2:55 The Rôle of the Pituitary in Carbohydrate Metabolism.
Carl F. Cori, St. Louis, Mo.

3:15 INTERMISSION.

4:00 Thyroid-Pituitary Relationship in Diabetes Insipidus.
Thomas P. Findley, Jr., St. Louis, Mo.

4:20 Some Recent Studies on Male Sex Hormones.
F. C. Koch, Chicago, Ill.

4:45 Experimental Work with the Female Sex Hormone.
E. A. Doisy, St. Louis, Mo.

5:10 ADJOURNMENT.

SECOND GENERAL SESSION

Monday evening, April 19, 1937

Presiding Officer

O. H. Perry Pepper, Philadelphia, Pa.

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p.m.

8:00 Daniel Drake.
Alfred Stengel, Philadelphia, Pa.

8:30 The Physician Himself as a Therapeutic Agent.
William R. Houston, Austin, Tex.

9:00 Protamine and Other Long-Acting Insulins.
Russell M. Wilder, Rochester, Minn.

9:30 The Rôle of Nutritional Deficiency States in Cardiac Decompensation.
Soma Weiss and Robert W. Wilkins, Boston, Mass.

10:00 The Importance of Ocular Signs in the Diagnosis of Brain Tumor.
Ernest Sachs, St. Louis, Mo.

10:30 ADJOURNMENT.

10:30 o'Clock

SMOKER

Ballroom, Jefferson Hotel

An interesting and amusing program has been arranged. Admission by registration badge.

THIRD GENERAL SESSION

Tuesday afternoon, April 20, 1937

Presiding Officer

James H. Means, Boston, Mass.

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p.m.

2:00 Practical Clinical Uses for Lactic Acid and Its Sodium Salt.
Alexis F. Hartmann, St. Louis, Mo.

2:25 Healed Bacterial Endocarditis.
Louis Hamman, Baltimore, Md.

2:45 The Relief of Certain Mental Symptoms by Operation on the Frontal Lobes with Observations upon Vasomotor and Visceral Manifestations.
Walter Freeman and James W. Watts, Washington, D. C.

3:15 INTERMISSION.
4:00 The Use of Para Amino Benzene Sulphonamide or Its Derivatives in the Treatment of Beta Hemolytic Streptococcal Infections.
Perrin H. Long and Eleanor A. Bliss, Baltimore, Md.
4:30 Bronchiogenic Carcinoma.
Evarts A. Graham, St. Louis, Mo.
5:00 ADJOURNMENT.

FOURTH GENERAL SESSION

Tuesday evening, April 20, 1937

Presiding Officer

Egerton L. Crispin, Los Angeles, Calif.

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p.m.
8:00 Remarks upon the Classification of Bright's Disease and Arterial Hypertension.
Willard J. Stone, Pasadena, Calif.
8:20 The Hereditary Factor in Essential Hypertension.
Edgar A. Hines, Jr., Rochester, Minn.
8:40 Further Studies in the Genesis and Surgical Treatment of Essential Hypertension.
George W. Crile, Cleveland, Ohio.
9:10 Experimental Hypertension Due to Renal Ischemia.
Harry Goldblatt, Cleveland, Ohio.
9:40 The Surgical Treatment of Peptic Ulcer.
Irvin Abell, Louisville, Ky.
10:00 ADJOURNMENT.

FIFTH GENERAL SESSION

Wednesday afternoon, April 21, 1937

Presiding Officer

David P. Barr, St. Louis, Mo.

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p.m.
2:00 The Clinical Caprices of Hodgkin's Disease.
William S. Middleton, Madison, Wis.
2:25 Hyperthyroidism in the Negro.
William B. Porter, Richmond, Va.
2:50 The Nutritional Factor in Graves' Disease.
James H. Means, Boston, Mass.

3:10 INTERMISSION.
3:55 Recent Knowledge Concerning Influenza.
Richard E. Shope, Princeton, N. J.
4:25 The Internist and Syphilis Control.
Hugh J. Morgan, Nashville, Tenn.
4:50 A Study of the Diagnosis and Treatment of Lobar Pneumonia According to Types and Specific Serum Therapy.
Julien E. Benjamin and Marion A. Blankenhorn, Cincinnati, Ohio.
5:10 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday evening, April 21, 1937

8:30 o'Clock

Ballroom, Jefferson Hotel

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. Presentation of newly elected Fellows and recital of the Pledge.
William Gerry Morgan, *Secretary-General*, Washington, D. C.
2. Conferring of Fellowships, and Address.
Ernest B. Bradley, *President*, Lexington, Ky.
3. Presentation of the John Phillips Memorial Medal for 1936–37.
4. Convocation Oration: "The Organism as a Unity."
John Dewey, Professor Emeritus of Philosophy, Columbia University, New York, N. Y.

President's Reception

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

SIXTH GENERAL SESSION

Thursday afternoon, April 22, 1937

Presiding Officer

William Gerry Morgan, Washington, D. C.

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p.m.
2:00 Bone Marrow Biopsies: A Development of the Diagnostic Procedure.
Edward L. Tuohy, Duluth, Minn.

2:20 The Differential Diagnosis and Therapeutic Rationale of Diseases Primarily Involving the Bone Marrow.
Charles A. Doan, Columbus, Ohio.

2:45 The Occurrence and Treatment of Arrhythmias in Coronary Artery Thrombosis.
Arthur M. Master, New York, N. Y.

3:10 Early Clinical Recognition of Disturbances in Heart and Blood Vessel Pathology—As Possible Solution to High Cardiac Mortality Rate.
Clarence L. Andrews, Atlantic City, N. J.

3:30 INTERMISSION.

4:15 What is Hypertrophic Arthritis?
Walter Bauer, Boston, Mass.

4:45 The American Board of Internal Medicine and Certification of Internists.
Walter L. Bierring, Des Moines, Iowa.

5:05 ADJOURNMENT.

The *Annual Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Important amendments to the Constitution and By-Laws of the College are to be presented for consideration and adoption. Official reports from the Treasurer and Executive Secretary will be read; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. James H. Means, will be inducted into office.

Thursday evening, 8:00 o'Clock

Ballroom, Jefferson Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster: Alfred Stengel, Philadelphia, Pa.
Address: "Medical Shrines."
Logan Clendening, Professor of Clinical Medicine, University of Kansas School of Medicine, Kansas City, Mo.

Dancing

SEVENTH GENERAL SESSION

Friday afternoon, April 23, 1937

Presiding Officer

Hugh J. Morgan, Nashville, Tenn.

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p.m.
2:00 The Dementia Precox Problem.
Gustave W. Dishong, Omaha, Nebr.

2:20 The Liver in Thyroid Disease.
Elmer C. Bartels, Boston, Mass.

2:50 Epigastric Hernia.
Louis A. M. Krause and David Tenner, Baltimore, Md.

3:15 INTERMISSION.

3:35 The Chemical Constitution of Gastric Juice and an Estimate of the Value of Gastric Secretory Studies in Clinical Medicine.
Lay Martin, Baltimore, Md.

3:55 Electrocardiographic Changes in Dogs Following External Injury.
Ray W. Kissane, Columbus, Ohio.

4:15 Ebstein's Disease or Congenital Dislocation of the Tricuspid Valve; Report of a Case with Intraventricular Conduction Disturbances Studied by Serial Sections Through the Conduction System.
Wallace M. Yater, Washington, D. C., and Morse J. Shapiro, Minneapolis, Minn.

4:35 ADJOURNMENT.

PROGRAM OF MORNING LECTURES

This course of Morning Lectures is a special feature on the program, arranged at the request of a large number of members. The course is presented as an elective, as a whole or for individual days, in place of hospital clinics. Those attending the lectures may also attend the Round Table Conferences. These lectures will be presented daily, Tuesday to Friday, inclusive, from 9:30 to 11:30 a.m. in the Ballroom of the Jefferson Hotel.

It is intended that the Morning Lectures shall be highly practical, and that the speakers will present their subjects with the aid of lantern slides, moving pictures and other demonstrations. They will consist of three symposia: Tuberculosis, Infectious Diseases and Diabetes Mellitus, and a mixed program.

The lectures will be open to all members of the College, guests of the College, members of the St. Louis Medical Society, Senior students of the medical schools of St. Louis and House Officers of participating hospitals. *Admission by regular registration badge.*

Tuesday Morning, April 20, 1937

ML 1 **JEFFERSON HOTEL**

Ballroom

Symposium on Tuberculosis

9:30–10:00 Recent Studies Bearing on Tuberculous Infection and Reinfection.
Henry C. Sweaney, Chicago, Ill.

10:00–10:30 Heliotherapy and Tuberculosis.
Edgar Mayer, New York, N. Y.

10:30–11:00 Surgical Measures in Treatment of Tuberculosis.
Ralph C. Matson, Portland, Ore.

11:00–11:30 The Prognosis in Tuberculosis.
F. M. Pottenger, Monrovia, Calif.

Wednesday Morning, April 21, 1937

ML 2 **JEFFERSON HOTEL**

Ballroom

Symposium on Infectious Diseases

9:30–10:00 Chronic Brucella Infections.
Fred E. Angle and William H. Algie, Kansas City, Kan.

10:00–10:30 The Clinical Types of Encephalitis.
Theodore C. Hempelmann, St. Louis, Mo.

10:30–11:00 Scarlet Fever.
Jean Valjean Cooke, St. Louis, Mo.

11:00–11:30 Meningococcic Meningitis and Meningococcemia.
Josephine B. Neal, New York, N. Y.

Thursday Morning, April 22, 1937

ML 3 **JEFFERSON HOTEL**

Ballroom

Symposium on Diabetes

9:30–10:00 Clinical Use of Crystalline Insulin.
Samuel S. Altshuler, Detroit, Mich.

10:00–10:30 Treatment of Diabetes Mellitus with Insoluble Insulin Compounds, II Histone-Insulin.
Percival A. Gray, Jr., Fritz Bischoff and William D. Sansum, Santa Barbara, Calif.

10:30–11:00 Factors Influencing the Prognosis in Diabetic Coma.
Edward S. Dillon and W. Wallace Dyer, Philadelphia, Pa.

11:00–11:30 The Hemopoietic Liver Principle.
George E. Wakerlin, Louisville, Ky.

Friday Morning, April 23, 1937

ML 4 **JEFFERSON HOTEL**

Ballroom

9:30–10:00 Sedimentation Rate of the Blood and Its Application in Clinical Medicine.
Edwin G. Bannick, Rochester, Minn.

10:00–10:30 Inquiries into the Fundamental Nature of Disease.
John W. Williams, Cambridge, Mass.

10:30–11:00 Subacute Bacterial Endocarditis: Active Cases with Negative Blood Cultures.
Chester S. Keefer, Boston, Mass.

11:00–11:30 The Less Common Varieties of Hypertension.
Maurice C. Pincoffs, Baltimore, Md.

ROUND TABLE CONFERENCES

This series of Round Table Conferences is a new feature on the program of the Annual Session of the College. These Round Tables have been scheduled at a time so as not to conflict with the Morning Lectures or the Hospital Clinics.

A national authority has been selected for each topic. Three Round Tables will be in progress simultaneously, and all will be held in adjoining rooms at the Jefferson Hotel, with the exception of the one on Pulmonary Tuberculosis, which will be held at the Park Plaza Hotel. The groups will necessarily be restricted in attendance.

Special tickets, similar to the Clinic tickets, will be required for each Round Table. When application is made for a Round Table it is strongly urged that the *applicant submit in writing a question or topic which he wishes discussed.* These questions will be given in advance to the Leaders of the Round Tables who will discuss such subjects as seem most in demand.

PROGRAM OF ROUND TABLES

Tuesday, April 20, 1937

JEFFERSON HOTEL

Second Floor, Room 9

(Capacity, 100)

12:00 m.–1:00 p.m. I. ROUND TABLE on Diabetes Mellitus.
Leader: Elliott P. Joslin, Clinical Professor of Medicine at the Harvard University Medical School; Medical Director of the George F. Baker Clinic, New England Deaconess Hospital; Boston, Mass.

JEFFERSON HOTEL

Second Floor, Room 8

(Capacity, 80)

12:00 m.–1:00 p.m. II. ROUND TABLE on the Public Health Aspects of Syphilis.
Leader: Thomas Parran, Surgeon-General, United States Public Health Service; President of the American Public Health Association; Washington, D. C.

JEFFERSON HOTEL

Second Floor, Room 7

(Capacity, 80)

12:00 m.–1:00 p.m. III. ROUND TABLE on Cardiovascular Problems.
Leader: Samuel A. Levine, Assistant Professor of

Medicine, Harvard University Medical School; Senior Associate in Medicine, Peter Bent Brigham Hospital; Boston, Mass.

Wednesday, April 21, 1937

PARK PLAZA HOTEL

(200 N. Kingshighway)
(near Washington University and Barnes Hospital)

(Capacity, 100)

12:15 p.m.–1:00 p.m. IV. ROUND TABLE on Pulmonary Tuberculosis.

Leader: James Alex. Miller, Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons; Visiting Physician and Physician in Charge of Tuberculosis Division, Bellevue Hospital; New York, N. Y.

Followed by luncheon as guests of the Trudeau Society of St. Louis.

JEFFERSON HOTEL

Second Floor, Room 9

(Capacity, 100)

12:00 m.–1:00 p.m. V. ROUND TABLE on Gastro-Enterologic Topics.

Leader: Walter C. Alvarez, Head of Section, Division of Medicine, The Mayo Clinic, and Professor of Medicine in the University of Minnesota, Graduate School of Medicine, Rochester, Minn.

JEFFERSON HOTEL

Second Floor, Room 8

(Capacity, 80)

12:00 m.–1:00 p.m. VI. ROUND TABLE on Amebiasis and Malaria, Diagnosis and Treatment.

Leader: Henry E. Meleney, Associate Professor of Preventive Medicine and Public Health, Vanderbilt University School of Medicine, Nashville, Tenn.

Thursday, April 22, 1937

JEFFERSON HOTEL

Second Floor, Room 7

(Capacity, 80)

12:00 m.–1:00 p.m. VII. ROUND TABLE on Allergy.
Leader: Robert A. Cooke, Assistant Professor of Clinical Medicine, Cornell University Medical College; Consultant in Medicine, New York Hospital; Director, Department of Allergy, Roosevelt Hospital; New York, N. Y.

JEFFERSON HOTEL

Second Floor, Room 9

(Capacity, 100)

12:00 m.–1:00 p.m. VIII. ROUND TABLE on Diseases of the Blood.
Leader: O. H. Perry Pepper, Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

JEFFERSON HOTEL

Second Floor, Room 8

(Capacity, 80)

12:00 m.–1:00 p.m. IX. ROUND TABLE on the Treatment of Various Phases of Syphilis.
Leader: Udo J. Wile, Professor of Dermatology and Syphilology, University of Michigan Medical School, Ann Arbor, Mich.

Please NOTE that all Round Tables are to be held at the Jefferson Hotel, except the Round Table on Tuberculosis, which is to be held at the Park Plaza Hotel.

SPECIAL CLINICS AND DEMONSTRATIONS

Clinics and demonstrations will be held in the forenoons from 9:30 to 12:00 daily, Tuesday to Friday, inclusive.

Tickets will be required for each and every one of the special clinics, ward rounds and demonstrations. The coöperation of every one in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each program. It is self-evident that an exercise arranged for fifteen will lose

its value for all if fifty crowd in. Ticket registration is the only effective method of keeping the attendance within the capacities indicated.

The clinics and demonstrations will be held in the Barnes Hospital, Firmin Desloge Hospital, Jewish Hospital, St. Luke's Hospital, St. Louis University Medical School and Washington University School of Medicine. The full detail of the program will be made available shortly after the appearance of this issue of the ANNALS. From the preliminary notices it is apparent that a very well organized series of clinical meetings will be offered by each institution. There are to be excellent symposia on allergy, endocrine diseases, peripheral vascular disease, hypertension, diseases of the blood, fever therapy, diabetes, diseases of the lungs, emphysema and numerous other clinics and demonstrations covering a wide range of topics in the infectious diseases, diseases of the digestive tract, of the nervous system, etc. In many of these features the staffs of the institutions concerned have added guest speakers of note from other parts of the country. It is felt that the clinical program of this meeting will meet or surpass the highest standards set in previous sessions of the College.